

Exhibit 41

African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates

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Abstract

Background: Risk factors for invasive epithelial ovarian cancer (IEOC) among Hispanics and African Americans are understudied despite notable differences in incidence relative to non-Hispanic whites.

Methods: We used multivariate logistic regression to examine parity, oral contraceptive use, tubal ligation, endometriosis, family history of ovarian cancer, and talc use and risk of IEOC among Hispanics (308 cases and 380 controls), African Americans (128 cases and 143 controls), and non-Hispanic whites (1,265 cases and 1,868 controls) using four case-control studies we conducted in Los Angeles County. We expressed each of these factors in the form of increasing risk and calculated population attributable risk percentage (PAR%) estimates for the six risk factors separately and jointly in the three groups.

Results: The risk associations with these six well-accepted factors were comparable in the three groups. The significant

racial/ethnic differences in the prevalence of these factors and differences in their oophorectomy rates explained 31% of the lower incidence in African Americans compared with non-Hispanic whites, but only 13% of the lower incidence in Hispanics. The PAR% ranged from 27.5% to 31.0% for no tubal ligation, 15.9% to 22.2% for not using oral contraceptives, and 12.2% to 15.1% for using talc in the three groups.

Conclusions: All six risk factors are comparably important in the three groups. Differences in the prevalence of these factors and their oophorectomy rates explained approximately one third of the difference in incidence between African Americans and non-Hispanic whites.

Impact: Devising strategies to lessen the burden of IEOC will be applicable to all three racial/ethnic groups. *Cancer Epidemiol Biomarkers Prev*; 24(7): 1094–100. ©2015 AACR.

Introduction

In the United States in the period 2000 to 2009, the annual age-adjusted incidence rate of invasive epithelial ovarian cancer (IEOC) was highest in non-Hispanic whites (14.3/100,000), intermediate in Hispanics (12.1/100,000; 15% lower than the rate in non-Hispanic whites) and lowest in African Americans (10.2/100,000; 29% lower than the rate in non-Hispanic whites; ref. 1). Epidemiologic studies of ovarian cancer risk have focused primarily on non-Hispanic white women; reasons for the racial/ethnic differences in incidence are not well understood.

A number of risk factors—first-degree family history of ovarian cancer, endometriosis, and use of talc—and protective factors—parity, use of oral contraceptives, and tubal ligation—have been unequivocally associated with ovarian cancer in non-Hispanic whites. There is virtually no information on ovarian cancer risk

factors in Hispanics. A small number of Hispanic cases ($n = 42$) were included in an ovarian cancer case-control study conducted in the Central Valley of California, but only results on talc use were reported separately in Hispanics (35.7% in cases vs. 26.9% in controls; ref. 2). A hospital-based case-control study in Mexico compared risk factors between 84 ovarian cancer cases and control women selected from an outpatient clinic (3): Parity and use of oral contraceptives were significantly inversely associated with risk but information on other factors has not been presented.

Risk factors for ovarian cancer among African Americans have been examined in three reports (4–6). The Collaborative Analysis of U.S. Case-Control Studies of Ovarian Cancer included seven studies with a total of 110 ovarian cancers (72 invasive, 35 borderline, and 3 unknown) in African-American women (4). Ness and colleagues (5) reported on risk of ovarian cancer among 84 African-American women with invasive or borderline cancers (numbers of each not specified) from their Delaware Valley case-control study. More recently, Moorman and colleagues (6) reported results from 111 African Americans with invasive ovarian cancer from their North Carolina ovarian cancer case-control study. Reduced risk from increased parity and oral contraceptive use were found in all three studies. Tubal ligation was found to be significantly inversely associated with risk in both of the studies that reported on this factor (5, 6). The results regarding family history are unclear. John and colleagues (4) did not report on family history. Ness and colleagues found that a family history of ovarian cancer was inversely associated with risk in African

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Americans, but this was based on sparse numbers (1.2% of cases vs. 2.0% of controls), a finding contrary to the strong increased risk found in non-Hispanic whites (4.6% of cases vs. 1.9% of controls; ref. 5). Family history of ovarian cancer was not reported in the North Carolina study, but family history of breast or ovarian cancer was a significant risk factor for African Americans (6).

The literature on causes of IEOC in Hispanics and African Americans is, therefore, very limited and it remains unclear to what extent the differences in the prevalence of ovarian cancer risk factors explain the differences in incidence between these three racial/ethnic groups. During the period 1992 to 2008, we conducted four IEOC case-control studies in Los Angeles County designed to elucidate risk factors for the disease and to evaluate differences in risk across non-Hispanic whites, Hispanics, and African Americans.

Materials and Methods

The results presented here are based on pooling the questionnaire data from these four studies, which used identical data collection methods as regards the factors discussed here; comprehensive details of these methods have been published (7–9). These studies were approved by the University of Southern California Institutional Review Board, and written informed consent was obtained from each patient and control before her interview.

Case ascertainment

For all studies, newly diagnosed histologically confirmed IEOC cases were identified from the USC Cancer Surveillance Program, which is the Los Angeles County SEER Program. Eligible patients were female residents of Los Angeles County of self-reported non-Hispanic white, Hispanic, or African-American race/ethnicity. Cases were eligible for inclusion in the study if they were between 18 and 74 years of age at diagnosis (up to age 79 for cases diagnosed between 2003 and 2008). A total of 3,370 patients met the study criteria (2,580 non-Hispanic whites, 506 Hispanics, 284 African Americans). Overall, 15.7% of patients (17.2% non-Hispanic whites, 8.5% Hispanics, and 15.5% African Americans) declined to be interviewed, 16.9% had died or were too ill to be interviewed (17.8% non-Hispanic whites, 12.1% Hispanics, and 17.6% African Americans), and 11.4% could not be located or had moved out of Los Angeles County (10.2% non-Hispanic whites, 14.0% Hispanics, and 17.6% African Americans). We were thus able to carry out in-person interviews with 1,886 patients (1,415 non-Hispanic whites, 331 Hispanics, and 140 African Americans), representing 63.2% participation rate of the patients approached (61.1% non-Hispanic whites, 76.1% Hispanics, and 59.8% African Americans). The response rate was higher for patients diagnosed with localized cancer (69%) compared with those with more advanced stage at diagnosis (61%). Response rates were highest for those diagnosed under age 60 (70%), intermediate for those ages 60 to 69 (59%), and lowest for those ages 70+ (47%) at diagnosis. In this analysis, we excluded 185 patients who had a previous cancer (excluding nonmelanoma skin cancer) or had prior bilateral oophorectomy and the final analysis was based on 1,701 patients (1,265 non-Hispanic whites, 308 Hispanics, and 128 African Americans).

Control ascertainment

Controls were residents of Los Angeles County with at least one intact ovary identified using a well-tested neighborhood control selection algorithm (8–10). Neighborhood controls were indi-

vidually matched to cases on race/ethnicity and year of birth (5 years); they represented essentially all the controls interviewed. In one study, selection of controls for cases >65 years of age was augmented, if necessary, by using lists of female residents of Los Angeles County provided by the Health Care Financing Administration, matched to the case on zip code, race/ethnicity, and year of birth closest to the case's year of birth (8). Overall, 70% of the non-Hispanic white, Hispanic, and African-American controls interviewed were the first identified control.

Data collection

In-person interviews were conducted using standardized questionnaires that included the use of a life calendar. The core questions on the risk factors presented here were identical in the four studies. The questionnaire covered events up to 12 months before a case's diagnosis date and a similar reference date for the controls.

The demographic, lifestyle, and medical history variables considered in this analysis include race/ethnicity (African American, Hispanic, and non-Hispanic white), age at diagnosis, parity, oral contraceptive use, tubal ligation, self-reported physician-diagnosed endometriosis, first-degree family history of ovarian cancer, and genital talc use.

Statistical analysis

We used standard statistical methods, including multivariate logistic regression, using the statistical package programs STATA 12 (StataCorp) and SAS 9.2 (SAS Institute Inc.). Although the studies were designed as matched case-control studies, at the termination of the particular studies, some cases had not been matched to a control and there were some controls whose cases had to be excluded after they completed the interview, because they were ineligible for the current analysis (e.g., not IEOC or did not live in Los Angeles County at the time of diagnosis). In this report, we have used all interviewed cases and controls by adopting a stratified multivariate logistic regression analysis approach with joint stratification for the three race/ethnicity groups, age group (<30, 5-year age groups to age 79), interviewer, and study. Analysis focused on the following factors: nulliparity (yes/no), oral contraceptive use (yes/no; no included never and <1 year of use), tubal ligation (yes/no), history of endometriosis (yes/no), family history of ovarian cancer (mother or sister; yes/no), and history of genital talc use (yes/no; no included never and <1 year of use). The logistic regression analysis also adjusted for menopausal status [premenopausal, natural menopause age 49, natural menopause age 50–54, natural menopause 55, surgical menopause (simple hysterectomy only) age 49, surgical menopause 50, other], age at menarche (11, 12, 13, 14), hormone therapy use (none, former or current estrogen + progestin, former or current estrogen alone), body mass index (BMI; kg/m²; 22, >22–24, >24–28, >28), family income (<40,000, >40,000 to <64,000, >64,000 to <100,000, >100,000, do not know) and education (high school or less, some college, college or higher). ORs—and corresponding 95% confidence intervals (CI)—were calculated as estimates of the relative risks (RR). All statistical significance values (*P* values) quoted are two-sided.

Population attributable risk percentages (PAR%), defined as the percentages of disease in the population that are attributable to a given risk factor (or set of risk factors), were calculated using the method of Bruzzi and colleagues (11). These authors showed that PAR% could be calculated from a case-control study using

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the estimated RRs applied to the cases only. This approach is of particular value to our analysis as it only requires the cases to be a representative sample from the population at risk. This method uses the individual data on each case to calculate the expected fraction of the cases that would not have occurred if the risk factors being considered were at their baseline values, and this fraction was then used to calculate the PAR%. For a single risk factor, the confidence limit for the PAR% was obtained by repeating the calculation using the lower (and upper) confidence bound of the OR for the particular factor in this calculation. For multiple risk factors, the confidence bounds for the PAR% were obtained by simulation: drawing repeated random samples from the mean and covariance matrix of the log ORs from the logistic regression fit and calculating a PAR% from that sample—the 95% CI bounds were taken as the 2.5% and 97.5% values from the repeated samples. In our simulation analyses, we used 5,000 repeats.

Published incidence rates for IEOC make no adjustment for the number of women who have had their ovaries (and fallopian tubes) removed. Writing h for the proportion of women who have had a hysterectomy and t for the proportion of hysterectomies that include removal of the ovaries (oophorectomy), an incidence rate r is approximately adjusted (not accounting for age at oophorectomy) for the oophorectomy rate as follows:

$$r_{\text{adj-ooph}} = r / (1 - h - t) \quad (\text{A})$$

If a population incidence rate (or an oophorectomy adjusted incidence rate) r is associated with a PAR% p for a single risk factor (or a group of risk factors) then the expected incidence rate if the population was at the baseline risk of the risk factor is:

$$r_{\text{adj-PAR}} = r \quad (1 - p/100) \quad (\text{B})$$

Results

This analysis was based on 1,701 women diagnosed with IEOC (1,265 non-Hispanic whites, 308 Hispanics, and 128 African Americans) and 2,391 control women (1,868 non-Hispanic whites, 380 Hispanics, and 143 African Americans). The distribution of IEOC by histology, stage at diagnosis and differentiation did not differ significantly between the three groups (Table 1). The majority of IEOC in the three racial/ethnic groups was of serous cell type, distant stage at diagnosis, and poorly differentiated.

The prevalence of the risk factors, including the average number of births, duration of oral contraceptive use, and duration of talc use in the three groups of controls and cases, are shown in Table 2. All six factors are presented in the manner of being associated with increasing risk; that is, the factors that are inversely associated with risk are presented in the form of their absence being a risk factor, for example, the decreased risk in parous women is presented as a risk in nulliparous women. This was done to allow the presentation of PAR% in a standard fashion.

With the exception of family history of ovarian cancer, the prevalence of the other risk factors differed significantly between the three racial/ethnic groups of control women (Table 2, top). The prevalence of no tubal ligation was 69.2% in African-American, 73.7% in Hispanic, and 85.9% in non-Hispanic white control women ($P_{2df} < 0.0001$). Nulliparity and history of endometriosis was highest in non-Hispanic whites, intermediate in African Americans, and lowest in Hispanics (23.7%, 16.8%, and 13.7% for nulliparity, $P_{2df} < 0.001$; 7.5%, 5.6%, and 3.4% for endometriosis, $P_{2df} = 0.008$). No oral contraceptive use (no/

Table 1. Tumor characteristics of invasive ovarian cancer in non-Hispanic whites, Hispanics, and African Americans: Los Angeles County Ovarian Cancer Study

	Non-Hispanic whites <i>N</i> = 1,265	Hispanics <i>N</i> = 308	African Americans <i>N</i> = 128
Age, y			
<30	12 (0.9%)	5 (1.6%)	1 (0.8%)
30–34	14 (1.1%)	11 (3.6%)	2 (1.6%)
35–39	33 (2.6%)	10 (3.2%)	3 (2.3%)
40–44	58 (4.6%)	31 (10.1%)	13 (10.2%)
45–49	144 (11.4%)	36 (11.7%)	17 (13.3%)
50–54	194 (15.3%)	60 (19.5%)	25 (19.5%)
55–59	186 (14.7%)	46 (14.9%)	18 (14.1%)
60–64	193 (15.3%)	43 (14.0%)	24 (18.8%)
65–69	179 (14.2%)	29 (9.4%)	15 (11.7%)
70–74	160 (12.6%)	23 (7.5%)	8 (6.3%)
75–79	92 (7.3%)	14 (4.5%)	2 (1.6%)
Histology			
Serous	721 (57.0%)	179 (58.1%)	71 (55.5%)
Mucinous	85 (6.7%)	26 (8.4%)	12 (9.4%)
Endometrioid	153 (12.1%)	34 (11.0%)	14 (10.9%)
Clear cell	75 (5.9%)	14 (4.5%)	4 (3.1%)
Epithelial	40 (3.2%)	13 (4.2%)	2 (1.6%)
Undifferentiated/poorly	53 (4.2%)	12 (3.9%)	10 (7.8%)
Other	131 (10.4%)	28 (9.1%)	14 (10.9%)
Not known	7 (0.6%)	2 (0.6%)	1 (0.8%)
$P_{3df}^{a,b}$		0.54	0.40
Stage			
Localized	216 (17.1%)	58 (18.8%)	30 (23.4%)
Regional	170 (13.4%)	49 (15.9%)	12 (9.4%)
Distant	853 (67.4%)	197 (64.0%)	83 (64.8%)
Not known	26 (2.1%)	4 (1.3%)	3 (2.3%)
$P_{2df}^{a,c}$		0.38	0.12
Differentiation			
Well	119 (9.4%)	29 (9.4%)	9 (7.0%)
Moderately well	235 (18.6%)	53 (17.2%)	28 (21.9%)
Poorly	502 (39.7%)	119 (38.6%)	46 (35.9%)
Undifferentiated	170 (13.4%)	33 (10.7%)	16 (12.5%)
Not known	239 (18.9%)	74 (24.0%)	29 (22.7%)
$P_{3df}^{a,b}$		0.81	0.63

^a P value comparing non-Hispanic whites with each of the other two groups separately.

^b P value based on cases of serous, mucinous, endometrioid, and clear-cell histology only.

^c P value excluding cases with no known histology or stage of cancer at diagnosis.

<1 year) was highest in Hispanics (54.7%), followed by African Americans (47.6%), and lowest in non-Hispanic whites (41.5%; $P_{2df} < 0.001$). Talc use was more common in African-American women (44.1%) than in non-Hispanic whites (30.4%) or Hispanics (28.9%; $P_{2df} = 0.001$). Similar patterns of differences in these risk factors between the three racial/ethnic groups of IEOC patients were found (Table 2, bottom).

As expected, each of the six risk factors had statistically significant independent effects on risk in non-Hispanic whites. Risk patterns in Hispanics paralleled those in non-Hispanic whites (Table 3), although the elevated risks with endometriosis and family history of ovarian cancer did not achieve statistical significance. In African Americans, family history of ovarian cancer was associated with a more than 7-fold increased risk, but the CI was wide (OR, 7.84; 95% CI, 1.66–37.0). The associations with parity, oral contraceptive use, tubal ligation, endometriosis, and talc use in African Americans are all in agreement with the risks found in non-Hispanic whites, although none were statistically significant.

Table 2. Prevalence of risk factors in non-Hispanic white, Hispanic, and African-American control women (top) and ovarian cancer cases (bottom)

Factors	Non-Hispanic whites	Hispanics	African Americans	P1 ^b	P2 ^c	P3 ^d
Controls^a						
Nulliparous (%)	23.7%	13.7%	16.8%	<0.001	0.076	0.45
Mean # births among parous (SD)	2.5 (1.3)	3.0 (1.7)	2.7 (1.5)	<0.001	0.03	0.15
Oral contraceptive use (no/<1 year; %)	41.5%	54.7%	47.6%	<0.001	0.19	0.17
Mean # months of OC use among users (SD)	95.9 (74.9)	81.0 (67.0)	93.1 (74.2)	0.014	0.75	0.21
No tubal ligation (%)	85.9%	73.7%	69.2%	<0.001	<0.001	0.36
Endometriosis (%)	7.5%	3.4%	5.6%	0.006	0.50	0.38
Family history of ovarian cancer (%)	2.5%	3.4%	2.8%	0.37	0.98	0.93
Talc use 1 year (%)	30.4%	28.9%	44.1%	0.61	0.0001	0.002
Mean # years of talc use among users (SD)	23.9 (17.4)	21.3 (16.7)	22.9 (17.0)	0.15	0.67	0.55
Cases^e						
Nulliparous (%)	27.8%	17.9%	16.4%	<0.001	0.007	0.82
Mean # births among parous (SD)	2.5 (1.2)	3.1 (1.7)	2.8 (1.6)	<0.001	0.003	0.24
Oral contraceptive use (no/<1 year; %)	57.4%	69.8%	50.0%	<0.001	0.13	<0.001
Mean # months of OC use among users (SD)	73.4 (61.1)	59.8 (53.1)	75.7 (66.7)	0.044	0.75	0.10
No tubal ligation (%)	90.6%	83.8%	80.5%	<0.001	<0.001	0.49
Endometriosis (%)	11.1%	5.5%	9.4%	0.005	0.66	0.21
Family history of ovarian cancer (%)	5.1%	4.9%	7.0%	0.96	0.48	0.50
Talc use 1 year (%)	41.2%	38.6%	47.7%	0.45	0.19	0.10
Mean # years of talc use among users (SD)	27.5 (18.4)	21.6 (16.9)	26.6 (18.2)	0.001	0.71	0.069

^aControls included: 1,868 non-Hispanic whites, 380 Hispanics, and 143 African Americans.

^bP_{1df} for differences between non-Hispanic whites and Hispanic controls (top)/P_{1df} for differences between non-Hispanic whites and Hispanic cases (bottom).

^cP_{1df} for differences between non-Hispanic whites and African American controls (top)/P_{1df} for differences between non-Hispanic whites and African American cases (bottom).

^dP_{1df} for differences between Hispanic and African American controls (top)/P_{1df} for differences between Hispanic and African American cases (bottom).

^eCases included: 1,265 non-Hispanic whites, 308 Hispanics, and 128 African Americans.

The adjusted ORs for the three racial/ethnic groups combined are also shown in Table 3.

The first three columns of Table 4 show that these six factors together accounted for 57.9% of IEOCs in non-Hispanic whites compared with 56.1% in Hispanics and 53.8% in African Americans based on the race/ethnicity-adjusted OR estimates shown in Table 3 (last column). The PAR% due to "no tubal ligation" was large in all three racial/ethnic groups, ranging from 27.5% to

31.0%, followed by "no oral contraceptive use" (ranging from 15.9% to 22.2%), and talc use (ranging from 12.2% to 15.1%). The PAR% for nulliparity was 8.9% in non-Hispanic whites, but lower in Hispanics (5.7%) and African Americans (5.5%). The PAR% for endometriosis (ranging from 2.0% to 4.0%) and family history of ovarian cancer (ranging from 2.7% to 3.9%) were more modest. The large "no tubal ligation" PAR% is due to relatively high prevalence in the IEOC patients (Table 2, bottom);

Table 3. Mutually adjusted ORs^a for invasive ovarian cancer in Los Angeles County non-Hispanic whites, Hispanics, and African Americans

	Non-Hispanic whites (1,265/1,868)			Hispanics (308/380)			African Americans (128/143)			All (1701/2391)		
	ca/co	OR (95% CI)		ca/co	OR (95% CI)		ca/co	OR (95% CI)		ca/co	OR (95% CI)	
Live-births												
Yes	913/1,426	1.00		253/328	1.00		107/119	1.00		1,273/1,873	1.00	
No	352/442	1.43 (1.19-1.73)		55/52	2.22 (1.28-3.84)		21/24	1.42 (0.54-3.75)		428/518	1.47 (1.24-1.75)	
Per birth		0.70 (0.58-0.84)			0.45 (0.26-0.78)			0.70 (0.27-1.86)			0.68 (0.57-0.81)	
Oral contraceptive (OC)												
Yes	539/1,092	1.00		93/172	1.00		64/75	1.00		696/1,339	1.00	
None/<1 year	726/776	1.55 (1.31-1.84)		215/208	1.29 (0.87-1.92)		64/68	1.30 (0.64-2.63)		1,005/1,052	1.47 (1.26-1.70)	
Per 5 years OC		0.64 (0.54-0.76)			0.77 (0.52-1.15)			0.77 (0.38-1.55)			0.68 (0.59-0.79)	
Tubal ligation												
Yes	119/263	1.00		50/100	1.00		25/44	1.00		194/407	1.00	
No	1,146/1,605	1.41 (1.10-1.81)		258/280	1.71 (1.07-2.74)		103/99	1.65 (0.73-3.74)		1,507/1,984	1.52 (1.23-1.87)	
Endometriosis												
No	1,125/1,728	1.00		291/367	1.00		116/135	1.00		1,532/2,230	1.00	
Yes	140/140	1.51 (1.15-1.98)		17/13	2.21 (0.89-5.48)		12/8	1.74 (0.45-6.74)		169/161	1.56 (1.21-2.00)	
First-degree family history of ovarian cancer												
No	1,200/1,822	1.00		293/367	1.00		119/139	1.00		1,612/2,328	1.00	
Yes	65/46	2.12 (1.40-3.21)		15/13	2.38 (0.94-6.01)		9/4	7.84 (1.66-37.0)		89/63	2.26 (1.58-3.25)	
Genital talc use												
None/<1 year	744/1,300	1.00		189/270	1.00		67/80	1.00		1,000/1,650	1.00	
Yes	521/568	1.41 (1.21-1.67)		119/110	1.77 (1.20-2.62)		61/63	1.56 (0.80-3.04)		701/741	1.46 (1.27-1.69)	
Per 5 years talc		1.14 (1.08-1.21)			1.18 (1.02-1.36)			1.15 (0.90-1.47)			1.14 (1.09-1.20)	

^aRace/ethnic specific multivariate logistic regression analyses were jointly stratified for age group (<30, 5-year age groups to age 79), interviewer and study, and adjusted for menopausal status, age at menarche, hormone therapy use, BMI, income, education, and each of the six factors shown. In analyses on "all subjects," we also jointly stratified by race/ethnicity.

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Table 4. Ovarian cancer PAR% and 95% CI in Los Angeles County non-Hispanic whites, Hispanics, and African Americans^a

	Using race-adjusted ORs ^a		
	Non-Hispanic whites PAR% ^b	Hispanics PAR% ^b	African Americans PAR% ^b
No live birth	8.9% 5.3%–11.9%	5.7% 3.4%–7.6%	5.3% 3.1%–7.0%
No/<1 year oral contraceptives	18.3% 12.0%–23.7%	22.2% 14.5%–28.8%	15.9% 10.4%–20.7%
No tubal ligation	31.0% 17.2%–42.3%	28.7% 15.9%–39.1%	27.5% 15.2%–37.5%
Yes endometriosis	4.0% 2.0%–5.5%	2.0% 1.0%–2.8%	3.4% 1.7%–4.7%
Yes family history ovarian cancer	2.9% 1.9%–3.6%	2.7% 1.8%–3.4%	3.9% 2.6%–4.9%
Yes/ 1 year talc use	13.0% 8.7%–16.8%	12.2% 8.1%–15.8%	15.1% 10.0%–19.5%
Three factors (no tubal ligation, no/<1 year oral contraceptives, yes/ 1 year talc use)	50.8% 39.7%–59.5%	51.2% 40.8%–59.3%	47.9% 37.8%–55.8%
All 6 factors	57.9% 48.7%–65.3%	56.1% 46.8%–63.3%	53.8% 45.0%–60.7%

^aUsing the all race/ethnicity adjusted ORs from Table 3.^bThe PARs were mutually adjusted for the variables shown in this table as well as for age group (<30, 5-year age groups to age 79), interviewer and study, menopausal status, age at menarche, hormone therapy use, BMI, income, and education.

it was 90.6% in non-Hispanic whites, 83.8% in Hispanics, and 80.5% in African Americans, so that a shift to the low-risk category, that is, having a tubal ligation, will have a substantial impact. In contrast, the PAR% due to nulliparity is lower because being parous is already highly prevalent; 72.2% in non-Hispanic whites, 83.6% in African Americans, and 82.1% in Hispanics, so that a shift to the low-risk category will have a lesser impact on the overall disease burden.

The mean number of births among parous IEOC cases was 2.5 in non-Hispanic whites, 2.8 in African Americans, and 3.1 in Hispanics (Table 2, bottom). We repeated the PAR% calculations after categorizing births as 0, 1, 2, 3, and 4+ using the 4+ category as baseline. The associated PAR% values increased as expected but the relationships of the PAR% by racial/ethnic group were essentially unaltered. Similarly, we categorized oral contraceptive use in finer categories of <1 year, 1 to 4 years, 5 to 9 years, and 10+ years with little effect on the relationships of the PAR% by racial/ethnic group (data not shown).

Discussion

With the high mortality and the lack of effective early screening for ovarian cancer, better understanding of preventive risk factors is a priority. The primary motivation for this analysis was to determine whether the six confirmed nongenetic risk factors for IEOC (parity, use of oral contraceptives, tubal ligation, endometriosis, first-degree family history of ovarian cancer, and use of genital talc) in non-Hispanic whites are also risk factors in Hispanics and African Americans. The risk patterns associated with these six factors were comparable in the three racial/ethnic groups (Table 3), and the PAR% for the factors jointly (Table 4) were also very similar.

An additional objective was to determine whether these six risk factors jointly could explain the 29% and 15% lower incidence of ovarian cancer in African Americans and Hispanics, respectively, compared with non-Hispanic whites. The incidence of ovarian cancer as reported by SEER, and other cancer registries, is calculated by considering all women in the denominator (population

at risk) without removing those who have had a bilateral oophorectomy and are not at risk. Thus, estimates of racial/ethnic differences in IEOC based on SEER data can be "improved" by accounting for the racial/ethnic differences in the prevalence of bilateral oophorectomy.

Although Lowder and colleagues (12) in their analysis of oophorectomy rates in women undergoing a hysterectomy in the National Hospital Discharge Survey covering the period 1979 to 2004, found that the proportion was approximately 40% and did not differ by racial/ethnic group; Jamison and colleagues (13) in their analysis of hysterectomy prevalence in women over age 50 in the Behavioral Risk Factor Surveillance System covering the years 1992 to 2008 found that the rate of hysterectomy was clearly higher in African-American women (47%) than in non-Hispanic whites (41%), and lower still in Hispanic women (36%). Using figures from these two studies in Equation A (see Statistical analysis) to adjust incidence rates for the proportion of women with a history of oophorectomy, we estimate that the observed 29% lower incidence rate in African Americans compared with non-Hispanic whites based on SEER data would be adjusted to 27% [$= 1 - 0.71 (1 - 0.41 - 0.4)/(1 - 0.47 - 0.4)$]. The PAR% of non-Hispanic whites was slightly higher at 57.8% than the PAR% in African Americans at 53.8% (Table 4); taking this into account, by use of Equation B (see Statistical analysis), reduced the difference in incidence between the two groups further from the adjusted 27% to 20%. Overall, taking into account the correction in the population at risk (denominator) and the PAR%, the difference in the African-American to non-Hispanic white incidence rates was reduced by 31% (1%–20%/29%). Given that hysterectomy rates are lower in Hispanics compared with non-Hispanic whites, Hispanics would be at even lower RR than what is observed in SEER; the 15% lower incidence rate in Hispanics compared with non-Hispanic whites would increase to 17% when using the correct at-risk denominator. The PAR% difference will change the difference slightly less in Hispanics compared with non-Hispanic whites from 17% to 13%. When taking into consideration the correct population at risk and the PAR%, the difference in incidence rates between Hispanics and non-Hispanic

whites is reduced by 13% (1%–13%/15%). Thus, this type of analysis suggests that further investigations are needed to identify other risk factors that may explain the remaining differences in IEOC rates between these three racial/ethnic groups.

Strengths of this study include the ability to evaluate the relative comparability in the effect of several well-established risk factors in non-Hispanics whites, Hispanics, and African Americans. Our results on Hispanics fill a knowledge gap, as this is the first study to examine etiologic risk factors for ovarian cancer in this growing minority population in the United States. Identical questionnaires and protocols were used in these four studies. Although information on these six factors was based on self-report, there is no evidence of systematic misclassification bias as the direction of racial/ethnic differences in the prevalence of tubal ligation, use of oral contraceptives, and endometriosis are consistent with other studies (6, 14–16). However, these results must be considered with caution as we were limited in that the sample sizes of Hispanics and African Americans were modest, and we investigated only the six factors that are confirmed, noncontroversial, showing strong associations with all invasive ovarian cancers in non-Hispanic whites. The modest sample sizes precluded us from conducting analyses separately by histologic type. The response rate for the three racial/ethnic groups was also modest, but not unlike the response rate for other case–control studies on ovarian cancer.

The comparable risk factor associations in IEOC in African Americans, Hispanics, and non-Hispanic whites contrast sharply with the more disparate risk factor patterns in breast cancer by race/ethnicity. A number of factors that are known to affect breast cancer risk in non-Hispanic whites do not appear to influence risk in African Americans and these differences cannot be explained by different prevalence of estrogen receptor/progesterone receptor-positive breast tumors between the two groups (17–21). Breast cancer risk factors also appeared to differ profoundly between Hispanics and non-Hispanic whites in one of the few studies with comparable data on both race/ethnic groups (15). Given the more comparable risk factor patterns in IEOC for non-Hispanic whites, Hispanics, and African Americans, devising strategies to lessen the burden of IEOC will be applicable to all groups.

Summary

Results from these population-based case–control studies suggest that the six well-established risk factors for IEOC accounted for about 60% of ovarian cancer risk in non-Hispanic whites, Hispanics, and African Americans. There were differences in the prevalence of these factors in the different racial/ethnic groups, and the 27% lower incidence of ovarian cancer in African Amer-

icans compared with non-Hispanic whites was reduced to 20% when these differences were adjusted for, but adjustment for these differences in prevalence accounted for only a very small amount of the lower incidence rate in Hispanics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.H. Wu, M.C. Pike

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.H. Wu, C.L. Pearce, C.-C. Tseng, M.C. Pike

Writing, review, and/or revision of the manuscript: A.H. Wu, C.L. Pearce, M.C. Pike

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.H. Wu

Study supervision: A.H. Wu, M.C. Pike

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Cancer Epidemiology, Biomarkers & Prevention

African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates

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Exhibit 42

OPEN

The Association Between Talc Use and Ovarian Cancer

A Retrospective Case–Control Study in Two US States

Daniel W. Cramer,^{Ab} Allison F. Vitonis,^A Kathryn L. Terry,^{Ab} William R. Welch,^C and Linda J. Titus^d

Background: Multiple studies of ovarian cancer and genital talc use have led only to conclusions about possible carcinogenicity. Seeking greater clarity, we examined this association in 2,041 cases with epithelial ovarian cancer and 2,100 age- and residence-matched controls. **Methods:** We defined genital talc use as regular application to the genital/rectal area directly, on sanitary napkins, tampons, or underwear to estimate “talc-years,” we multiplied application frequency by years used. Unconditional logistic regression with stratification, likelihood-ratio tests, and polynomial logistic regression were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI), trends, effect modification, and heterogeneity by ovarian cancer histologic subtype. **Results:** Overall, genital talc use was associated with an OR (95% CI) of 1.33 (1.16, 1.52), with a trend for increasing risk by talc-years. Women who used talc were more likely to be older, heavier, asthma sufferers, and regular anal users—none of which was a confounder. Dose–response was more apparent for premenopausal women especially nonsmokers and those heavier or postmenopausal users of menopausal hormones (hormone therapy [HT]). Subtypes of ovarian cancer more likely to be associated with talc included invasive serous and endometrioid tumors and borderline serous and mucinous tumors. Premenopausal women and postmenopausal HT users with these subtypes who had accumulated >24 talc-years had ORs (95% CI) of 2.33 (1.32, 4.12) and 2.57 (1.51, 4.36), respectively.

Conclusion: Risks for epithelial ovarian cancer from genital talc use vary by histologic subtype, menopausal status at diagnosis, HT use, weight, and smoking. These observations suggest that estrogen and/or prolactin may play a role in macrophage activity and inflammatory response to talc.

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In the 1960s, a link between talc and ovarian cancer was suggested by observations that some talc powders contained asbestos¹ and that asbestos placed in the peritoneally in animals transformed the single layer of the ovarian surface to a multilayered one with abnormal cells.² A 1971 study found particles compatible with talc in human ovarian and uterine cancers.³ A 1982 case–control study was the first to link genital talc use with ovarian cancer.⁴ Dozens more followed confirming the association including some larger ones cited here.^{5–13} The most recent meta-analysis reported a summary odds ratio (OR) and 95% confidence interval (CI) of 1.35 (1.26, 1.46).¹⁴ In 2006, the International Agency for Research on Cancer declared that talc used genitally is possibly carcinogenic.¹⁵ However, a study with null results from the Women's Health Initiative (WHI)¹⁶ and accompanying editorial¹⁷ cast new skepticism on the association here, we present data from combined phases of a case–control study of ovarian cancer involving more than 4,000 women to provide fresh perspectives on this association.

METHODS

Study Population

Data come from three enrollment phases: 1 (1992–1997), 2 (1998–2002), and 3 (2003–2008). Articles we previously published related to talc include a detailed report from phase 1,⁷ data from phases 1 and 2 combined with Nurses' Health Study data,¹⁸ and phases 1–3 data combined with data from several participants in the Ovarian Cancer Association Consortium (OCAC).¹⁹ This is the first detailed examination of talc data from the combined phases of our study.

Details regarding enrollment are described elsewhere.²⁰ In brief, 3,957 women residing in Massachusetts and New Hampshire diagnosed with ovarian cancer between ages 18 and 80 were identified through tumor boards and registries.

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Dr Cramer reports being paid for expert testimony in litigation related to ovarian cancer. Ms. Vitonis reports being paid for programming work related to the same litigation. The other authors have no conflicts to report.

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Eight hundred and seventy-four cases were ineligible if they had died, moved outside study area, did not have a working telephone number, or had a nonovarian primary tumor. Of the remaining 3,083 cases, 2,203 (71%) were enrolled. Excluding 127 nonepithelial and 35 mixed mesodermal tumors, 2,041 cases with epithelial tumors of ovarian, primary peritoneal, and Fallopian tube origin, including borderline malignancies (henceforth, epithelial ovarian cancer) were included. Pathology reports were reviewed and histologic subtype, grade, and stage recorded. Mixed epithelial ovarian cancer was classified as the predominant type. Undifferentiated, transitional cell, fallopian tube, or primary peritoneal tumors were counted as serous.²¹ Other mixed epithelial (n = 102), malignant Brenner (n = 5), and unspecified epithelial tumors (n = 27) were classified as other.

Controls were identified through random digit dialing, driver-license lists, and town-resident lists. Between 1992 and 1997, 420 (72%) identified through random digit dialing and 102 (51%) through lists agreed to participate. From 1998 to 2008, 4,366 potential controls were identified using the lists, of whom 1,426 (33%) were ineligible if they had died, moved, or were seriously ill or if they did not have a working telephone, speak English, or have ovaries. Of eligible controls, 1,362 (46%) declined to participate by phone or via “opt-out” postcard and 1,578 (54%) were enrolled (2,100 total). Controls were frequency matched to cases by 5-year age groups and region of residence.

Exposure Assessment

Subjects were personally interviewed about potential ovarian cancer risk factors that occurred more than 1 year before diagnosis, for cases, and interview, for controls. Subjects were asked whether they “regularly” or “at least monthly” applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital-rectal area. Additional details included type of powder, age begun, years used, and applications per month. Lifetime exposure was estimated by multiplying frequency of applications per month by months used. This was divided by 360 (i.e., daily use coded as 30/month) to yield talc-years. To create categorical variables for talc-years, we chose cut points based on quartiles for exposed controls and rounded to the nearest integer. In addition, we asked participants if their partners dusted or sprayed powder to their genital or rectal areas. Condom and diaphragm use as potential sources of talc exposure were also recorded.

We calculated ovulatory cycles by subtracting age at menarche from age at last period, reduced this by time spent pregnant, breastfeeding, or using oral contraceptives, and dividing the remainder by each woman’s average cycle length. Family history was defined as a mother or sister with ovarian or premenopausal breast cancer. Women who reported postmenopausal hormone use were classified as hormone therapy (HT) users and type(s) of HT was recorded. Participants

completed a food-frequency questionnaire²² from which grams of alcohol consumed per day were estimated.

Statistical Methods

Unconditional logistic regression was used to model the OR and 95% CI adjusted first for matching factors (age, study center, and phase) and then fully by potential confounders. Likelihood ratio tests comparing models with and without interaction terms were used to test for effect modification. Tests for trend were based on the Wald statistic using continuous variables weighted by category midpoints with zero assigned as the exposure for nonusers. Polytomous logistic regression was used to simultaneously estimate separate ORs and 95% CIs for genital talc use by histologic subtypes. Likelihood-ratio tests were used to calculate *P* values for heterogeneity by comparing polytomous logistic regression models in which the talc association was held constant over case subgroups to models that allowed the association to differ between case subgroups.²³ Analyses were performed using SAS v9.3 (SAS Institute, Cary, NC) and polytomous logistic regression analyses were performed in Stata (StataCorp LP, College Station, TX). Sensitivity analyses to assess the influence of exposure misclassification were performed with Excel using quantitative analysis methods described previously.²⁴

Ethical Approval

Institutional review boards approved the study. All participants provided written informed consent.

RESULTS

Genital use of talc, either alone or in combination with body use, was associated with elevated epithelial ovarian cancer risk (Table 1). Among women with no personal use, there was no increased risk with potential exposure from diaphragms, condoms, or partner use. Therefore, only those with personal genital talc exposure were classified as ever-users. Genital talc use was associated with an OR (95% CI) of 1.33 (1.16, 1.52) adjusted only for age, study center, and phase. Most women reported using Johnson & Johnson’s Baby Powder or Shower to Shower. Fourteen women who reported exclusive use of a cornstarch-based powder were considered unexposed. The average age women began using talc was 20.0 for cases and 19.8 for controls. Almost half of users were currently using or had only recently discontinued powder use at the reference date. Risk decreased with increased time since last use. The trend for frequency of use was significant, but the trend for years used was flat. Some subjects reported they used talc only seasonally, but our original questionnaire did not capture this detail. A question to capture months-per-year-used was added in 1998 and was available for 54% of cases and 56% of controls. Year-round use was the most common pattern, and more cases than controls used powder year-round. ORs for talc-years among those who reported months-per-year-used are shown as the next-to-final entry in Table 1. An OR of 1.49 (95% CI = 1.06, 2.10) was associated with more

TABLE 1. Type, Timing, and Duration of Genital Talc Use

	Control Subjects N (%)	Case Subjects N (%)	Adjusted ^a OR (95% CI)
PERSONAL USE			
None	1,099 (52)	1,001 (49)	1.00 (REFERENCE)
Body use ONLY	452 (22)	398 (20)	0.99 (0.84, 1.16)
GENITAL use ONLY	74 (4)	94 (5)	1.42 (1.04, 1.96)
Body AND GENITAL USE	475 (23)	548 (27)	1.30 (1.12, 1.52)
POTENTIAL EXPOSURE IN WOMEN WITH NO PERSONAL USE			
None	447 (41)	461 (46)	1.00 (REFERENCE)
DIAPHRAGM ONLY	207 (19)	155 (15)	0.73 (0.57, 0.93)
Condoms, with or without Diaphragm	367 (33)	308 (31)	0.82 (0.66, 1.01)
PARTNER USE, with or without Diaphragm or Condoms	78 (7)	77 (8)	0.96 (0.68, 1.35)
Any GENITAL powder USE			
No	1,551 (74)	1,399 (69)	1.00 (REFERENCE)
YES	549 (26)	642 (31)	1.33 (1.16, 1.52)
Type of GENITAL powder USE			
No GENITAL USE	1,542 (73)	1,394 (68)	1.00 (REFERENCE)
CONDOM USE ONLY	9 (<1)	5 (<1)	0.58 (0.19, 1.74)
Johnson AND Johnson NB/My Powder OR Shower To Shower	316 (15)	363 (18)	1.30 (1.10, 1.54)
OTHER BRAND(s)	233 (11)	279 (14)	1.35 (1.12, 1.64)
AGE FIRST USED GENITAL powder			
NEVER USED	1,551 (74)	1,399 (69)	1.00 (REFERENCE)
<20	343 (16)	363 (18)	1.19 (1.01, 1.41)
20–29	122 (6)	183 (9)	1.71 (1.34, 2.17)
≥30	76 (4)	87 (4)	1.31 (0.95, 1.80)
TIME SINCE EXPOSURE ENDED			
No GENITAL USE	1,551 (74)	1,399 (69)	1.00 (REFERENCE)
≥35 YEARS	51 (2)	52 (3)	1.18 (0.79, 1.75)
25–34 YEARS	81 (4)	88 (4)	1.24 (0.91, 1.70)
15–24 YEARS	72 (3)	82 (4)	1.30 (0.94, 1.80)
5–14 YEARS	79 (4)	95 (5)	1.36 (1.00, 1.85)
CURRENTLY USING OR RECENTLY STOPPED	255 (12)	314 (15)	1.38 (1.15, 1.65)
P TEND			<0.0001
FREQUENCY OF USE			
No GENITAL USE	1,551 (74)	1,399 (69)	1.00 (REFERENCE)
1–7 days PER MONTH	220 (11)	227 (11)	1.17 (0.96, 1.44)
8–29 days PER MONTH	110 (5)	133 (7)	1.37 (1.05, 1.78)
≥30 days PER MONTH	205 (10)	267 (13)	1.46 (1.20, 1.78)
P TEND			<0.0001
YEARS USED			
NEVER USED	1,551 (74)	1,399 (69)	1.00 (REFERENCE)
<8	133 (6)	152 (8)	1.31 (1.03, 1.68)
8–19	126 (6)	145 (7)	1.31 (1.02, 1.68)
20–35	147 (7)	178 (9)	1.35 (1.07, 1.70)
>35	129 (6)	152 (7)	1.33 (1.03, 1.71)
P TEND			0.002
MONTHS PER YEAR OF USE ^c			
No GENITAL USE	1,551 (83)	1,399 (80)	1.00 (REFERENCE)
1–3 months PER YEAR	61 (3)	60 (3)	1.11 (0.77, 1.61)
4–11 months PER YEAR	55 (3)	56 (3)	1.13 (0.77, 1.66)
12 months PER YEAR	193 (10)	229 (13)	1.35 (1.09, 1.67)
P TEND			0.006

(Continued)

TABLE 1. (Continued)

	Control Subjects N (%)	Case Subjects N (%)	Adjusted ^a OR (95% CI)
Total genital talc applications (apps) among only those who reported months per year of use ^c			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	106 (6)	103 (6)	1.10 (0.83, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	79 (4)	96 (5)	1.38 (1.01, 1.88)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	61 (3)	63 (4)	1.16 (0.80, 1.66)
>7,200 apps (equivalent to >20 years of daily use)	63 (3)	83 (5)	1.49 (1.06, 2.10)
<i>P</i> trend			0.02
Total genital talc applications among all (assuming 12 months/year when missing months per year of use)			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	138 (7)	138 (7)	1.15 (0.89, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	124 (6)	148 (7)	1.36 (1.06, 1.75)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	124 (6)	156 (8)	1.41 (1.10, 1.80)
>7,200 apps (equivalent to >20 years of daily use)	149 (7)	185 (9)	1.39 (1.11, 1.75)
<i>P</i> trend			0.003

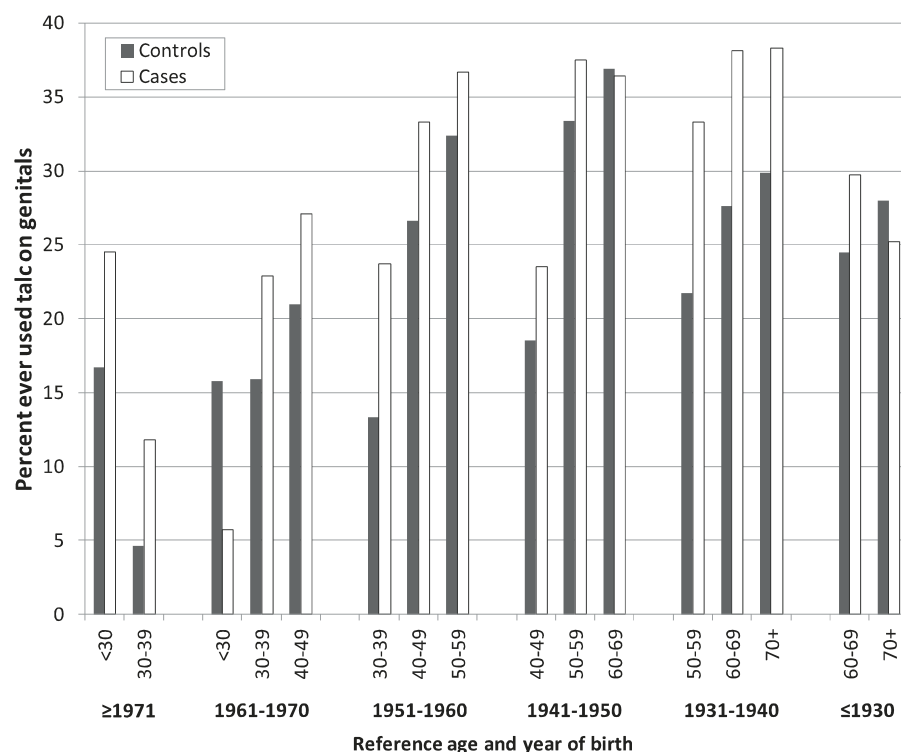
^aAdjusted only for the study matching factors: reference age, study center, and study phase.^bNine cases and nine controls reported they knew that talc had been used on them in infancy so their age at exposure was recorded as 1.^cExcludes talc users from phase 1 and part of phase 2 because months/year of use was not collected.

FIGURE 1. Proportions of cases and controls who ever used talc on genitals in categories by decade of birth and reference age.

than 20 talc-years (>7,200 applications) and a dose-response.

For subjects missing the seasonal-use variable, we assumed 12 months per year in calculating talc-years in the final entry in Table 1, as well as in subsequent tables and figures examining talc-years. Even with this imprecision, the trend remained, although the increase was less monotonic.

Figure 1 shows the proportions of cases and controls who used talc in the genital area by decade of birth and age at

diagnosis or interview. In 13 of the 16 age-and-birth categories, a greater proportion of cases used talc compared with controls. This suggests that the association between genital use of talc and epithelial ovarian cancer is not confined to any particular age or birth cohort.

Powder users, both cases and controls, were more likely to be older, heavier, asthma sufferers, and regular analgesic users (Table 2). By tests for interaction (column 3), the

TABLE 2. Illustrating Potential Effect Modification and Confounding

	Controls		Cases		Stratum-specific OR (95% CI) ^a for Genital Talc Use	P Int ^b	OR (95% CI) for Genital Talc Use Adjusted ^c
	No Genital Talc Use N (%)	Any Genital Talc Use N (%)	No Genital Talc Use N (%)	Any Genital Talc Use N (%)			
AGE							
<50	670 (80)	165 (20)	600 (74)	211 (26)	1.42 (1.13, 1.80)	0.63	1.30 (1.13, 1.49) ^d
50–64	599 (68)	278 (32)	541 (64)	308 (36)	1.25 (1.03, 1.53)		
≥65	282 (73)	106 (27)	258 (68)	123 (32)	1.35 (0.98, 1.85)		
STudy CENTER							
NEw HAMpshIRE	319 (82)	72 (18)	316 (74)	109 (26)	1.52 (1.08, 2.14)	0.30	1.31 (1.15, 1.50) ^e
MAssACHuSETTS	1,232 (72)	477 (28)	1,083 (67)	533 (33)	1.29 (1.11, 1.50)		
STudy phASe							
1	430 (82)	92 (18)	409 (73)	149 (27)	1.71 (1.27, 2.30)	0.12	1.33 (1.16, 1.52) ^f
2	519 (72)	202 (28)	448 (68)	210 (32)	1.23 (0.97, 1.55)		
3	602 (70)	255 (30)	542 (66)	283 (34)	1.25 (1.02, 1.54)		
RACE							
WHITE	1,500 (74)	531 (26)	1,321 (68)	612 (32)	1.35 (1.17, 1.55)	0.002	1.33 (1.16, 1.53)
AFRICANAmERICAN	17 (74)	6 (26)	16 (46)	19 (54)	5.08 (1.32, 19.6)		
HISPANIC	27 (82)	6 (18)	25 (81)	6 (19)	1.10 (0.30, 4.12)		
ASIAN	5 (50)	5 (50)	34 (94)	2 (6)	0.04 (0.01, 0.34)		
OTHER	2 (67%)	1 (33)	3 (50)	3 (50)	-		
Body mass INDEX							
<24.9	798 (76)	251 (24)	727 (72)	284 (28)	1.25 (1.03, 1.53)	0.59	1.32 (1.15, 1.51)
≥24.9	753 (72)	298 (28)	672 (65)	358 (35)	1.38 (1.14, 1.67)		
HEIGHT(m)							
<1.63	755 (73)	283 (27)	689 (68)	325 (32)	1.28 (1.06, 1.56)	0.71	1.32 (1.16, 1.52)
≥1.63	795 (75)	266 (25)	710 (69)	317 (31)	1.37 (1.13, 1.66)		
WEIGHT(lbs)							
<148	799 (77)	241 (23)	727 (73)	272 (27)	1.24 (1.01, 1.52)	0.58	1.32 (1.15, 1.51)
≥148	745 (71)	307 (29)	670 (64)	370 (36)	1.38 (1.15, 1.66)		
PARTY							
NullipARous	284 (75)	94 (25)	455 (70)	195 (30)	1.28 (0.96, 1.71)	0.71	1.33 (1.15, 1.52)
PARous	1,267 (74)	455 (26)	944 (68)	447 (32)	1.34 (1.15, 1.57)		
EverBleEDed							
No	781 (72)	296 (28)	953 (69)	430 (31)	1.21 (1.01, 1.45)	0.16	1.30 (1.13, 1.50)
YES	770 (75)	253 (25)	446 (68)	212 (32)	1.48 (1.19, 1.85)		
ORALCoNIRAcEpTivEusE							
NEVERoR<3 moNths	559 (73)	207 (27)	672 (69)	302 (31)	1.25 (1.01, 1.55)	0.38	1.32 (1.15, 1.51)
≥3 moNths	992 (74)	342 (26)	727 (68)	340 (32)	1.39 (1.16, 1.67)		
INTRAUTERINEdEvICEusE							
No	1,300 (74)	447 (26)	1,203 (69)	547 (31)	1.35 (1.16, 1.56)	0.59	1.33 (1.16, 1.52)
YES	251 (71)	102 (29)	196 (67)	95 (33)	1.20 (0.85, 1.70)		
OvULAToRy CyCLES							
<366	748 (78)	214 (22)	542 (74)	191 (26)	1.28 (1.02, 1.61)	0.76	1.31 (1.14, 1.52)
≥366	680 (71)	281 (29)	733 (65)	402 (35)	1.37 (1.13, 1.65)		
ENDometRIosIs oRPAInFuLpERods							
No	1,006 (74)	345 (26)	814 (70)	351 (30)	1.29 (1.08, 1.55)	0.77	1.31 (1.14, 1.50)
YES	545 (73)	204 (27)	585 (67)	291 (33)	1.35 (1.09, 1.67)		
JBvIsh EfFECt							
No	1,455 (74)	518 (26)	1,277 (69)	585 (31)	1.33 (1.15, 1.53)	0.72	1.33 (1.16, 1.52)
YES	96 (76)	31 (24)	122 (68)	57 (32)	1.39 (0.83, 2.33)		

(Continued)

TABLE 2. (Continued)

	Controls		Cases		Stratum-specific OR (95% CI) ^a for Genital Talc Use	P Int ^b	OR (95% CI) for Genital Talc Use Adjusted ^c
	No Genital Talc Use N (%)	Any Genital Talc Use N (%)	No Genital Talc Use N (%)	Any Genital Talc Use N (%)			
Family history ^G							
No	1,446 (74)	510 (26)	1,267 (68)	585 (32)	1.34 (1.16, 1.55)	0.61	1.33 (1.16, 1.52)
Yes	105 (73)	39 (27)	132 (70)	57 (30)	1.19 (0.73, 1.93)		
PERSONAL history of BREASTCANCER							
No	1,498 (74)	519 (26)	1,299 (68)	606 (32)	1.38 (1.20, 1.59)	0.01	1.33 (1.16, 1.53)
Yes	53 (64)	30 (36)	100 (74)	36 (26)	0.67 (0.37, 1.22)		
History of TUBAL LIGATION							
No	1,135 (74)	401 (26)	1,134 (70)	480 (30)	1.22 (1.04, 1.43)	0.02	1.34 (1.16, 1.53)
Yes	416 (74)	148 (26)	265 (62)	162 (38)	1.73 (1.31, 2.27)		
Menopausal status AND HT							
Premenopausal	735 (79)	197 (21)	653 (73)	247 (27)	1.41 (1.13, 1.75)	<0.001	1.33 (1.16, 1.53)
Postmenopausal, No HT	507 (69)	230 (31)	549 (70)	238 (30)	0.97 (0.78, 1.20)		
Postmenopausal, HT	309 (72)	122 (28)	197 (56)	157 (44)	2.21 (1.63, 3.00)		
Current smoking							
No	1,332 (74)	473 (26)	1,149 (68)	538 (32)	1.35 (1.16, 1.56)	0.60	1.32 (1.16, 1.52)
Yes	219 (74)	76 (26)	250 (71)	104 (29)	1.19 (0.84, 1.69)		
Ever smoked							
No	759 (75)	248 (25)	669 (70)	291 (30)	1.34 (1.10, 1.64)	0.72	1.32 (1.16, 1.52)
Yes	792 (72)	301 (28)	730 (68)	351 (32)	1.31 (1.09, 1.58)		
Aspirin use							
No	1,442 (75)	492 (25)	1,310 (69)	586 (31)	1.34 (1.16, 1.55)	0.70	1.33 (1.16, 1.52)
Yes	109 (66)	57 (34)	89 (61)	56 (39)	1.25 (0.78, 2.01)		
Alcohol (grams per day)							
≤2.32	753 (74)	269 (26)	738 (70)	311 (30)	1.19 (0.98, 1.45)	0.29	1.30 (1.13, 1.50)
>2.32	763 (75)	259 (25)	623 (68)	291 (32)	1.43 (1.17, 1.75)		
Any acetaminophen use							
No	1,190 (76)	373 (24)	1,076 (71)	431 (29)	1.30 (1.10, 1.53)	0.83	1.32 (1.15, 1.52)
Yes	361 (67)	176 (33)	323 (60)	211 (40)	1.41 (1.09, 1.82)		
Any aspirin or ibuprofen use							
No	936 (77)	285 (23)	901 (71)	361 (29)	1.32 (1.10, 1.59)	0.94	1.34 (1.17, 1.53)
Yes	615 (70)	264 (30)	498 (64)	281 (36)	1.36 (1.11, 1.68)		
Adjusted for ALL variables	1,551	549	1,399	642	-	-	1.32 (1.15, 1.53)

^aAdjusted for REFERENCE AGE (CONTINUOUS), study CENTER AND study phase.^bP for INTERACTION from likelihood ratio tests comparing models with MAIN EFFECTS AND INTERACTION TERMS to models with MAIN EFFECTS only.^cAdjusted for REFERENCE AGE (CONTINUOUS), study CENTER, study phase, AND EACH variable listed (individually). BMI, height, weight, AND ovulatory cycles were adjusted for with INDICATORS for quartiles AND parity (Nulliparous, 1, 2, ≥2), breastfeeding (never <4, 4–9, 10–19, >19 months), AND OC use (never <23, 23–49, 50–96, >96 months) were adjusted for with INDICATORS for categories.^dAdjusted for REFERENCE AGE only.^eAdjusted for REFERENCE AGE AND study CENTER.^fAdjusted for REFERENCE AGE, study CENTER, AND study phase.^gFamily history of ovarian or early onset breast cancer in a mother or sister.

ASSOCIATION WAS SIGNIFICANTLY GREATER FOR WOMEN WHO WERE AFRICAN AMERICAN HAD NO PERSONAL HISTORY OF BREASTCANCER, HAD A TUBAL LIGATION OR HYSTERECTOMY, WERE PREMENOPAUSAL, OR WERE POSTMENOPAUSAL AND USED HT. THE LATTER FINDING TOGETHER WITH THE DOSE-RESPONSE DATA IS ILLUSTRATED IN FIGURE 2. AMONG THE HT USERS, 92% USED ESTROGEN (ALONE OR IN COMBINATION), 2% USED PROGESTERONE ALONE, AND 5% USED CREAMS OR SUPPOSITORIES. INCREASED EPITHELIAL OVARIAN CANCER RISK WITH GENITAL TALC

USE WAS FOUND IN BOTH WOMEN WHO HAD USED ESTROGEN ALONE OR ESTROGEN PLUS PROGESTERONE. TOO FEW WOMEN USED PROGESTERONE ONLY, HT OR ESTROGEN CREAMS OR SUPPOSITORIES TO EXAMINE RISK WITH TALC USE IN THESE GROUPS (DATA NOT SHOWN). THE MEDIAN DURATION OF HT USE WAS 5 YEARS. SUBJECTS WITH <5 YEARS OF HT USE HAD AN OVERALL OR (95% CI) FOR EOC RISK WITH EVER USE OF TALC ON GENITALS OF 2.93 (1.86, 4.62). SUBJECTS WITH ≥5 YEARS OF HT USE HAD AN OR (95% CI) THAT WAS SLIGHTLY LOWER, 1.73

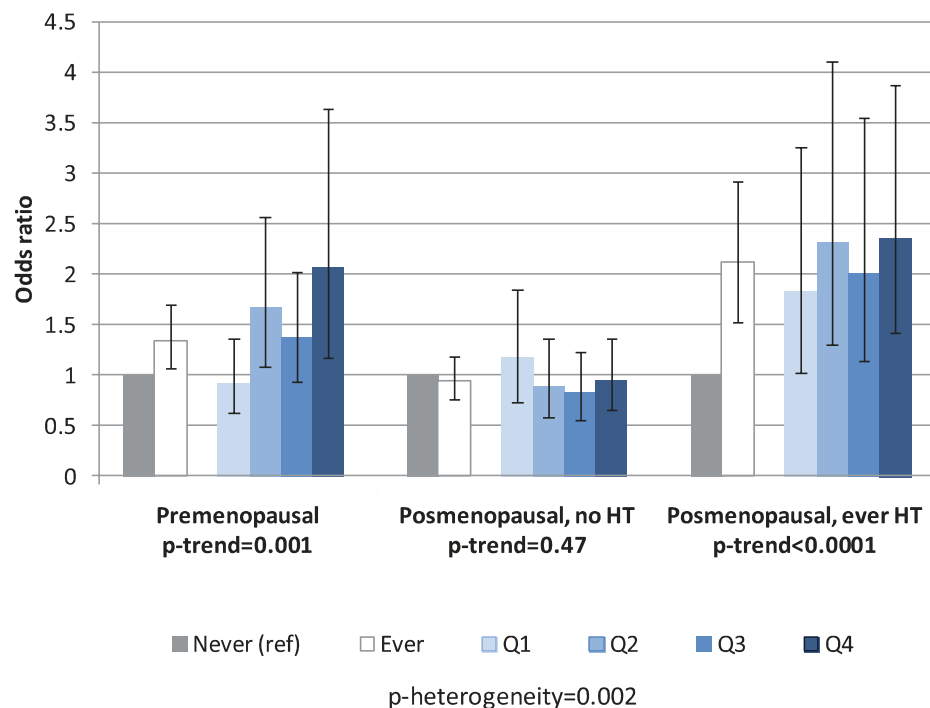


FIGURE 2. Associations between use of talc on genitals (never/ever and quartiles of talc-years) and ovarian cancer by menopausal status and postmenopausal hormone therapy.

(1.15, 2.62), but a clear trend for increasing risk with talc-years was more apparent in the longer-term HT users (data not shown). To explore the potential interaction between talc use and hysterectomy or tubal ligation, we restricted this analysis to subjects who had either or both procedures (Table 3). For premenopausal women, risk for EOC was increased in women who used talc before the procedure, while risk was elevated for use both before and after the procedure in postmenopausal women who used HT. No associations were seen in postmenopausal women who had not used HT. There were too few subjects who had used talc only after hysterectomy or tubal ligation to permit reliable estimates of risk.

Returning to Table 2, we applied the convention that a variable may be a confounder if adjusting yields a 10% difference compared with the crude OR (or, in our study, compared with the OR of 1.33 adjusted for age, study center and study phase). A 10% lower or greater chance corresponds to an OR ≤ 1.20 or ≥ 1.46 . As seen in the far right column, the OR of 1.33 for ovarian cancer risk was not materially changed after adjusting for any individual covariables.

Because Figure 2 suggests that EOC risk with talc varies by menopausal status, we revisited the issue of interaction in Table 1 (<http://links.lww.com/EDE/B2>) in which subjects are stratified by menopausal status. Although few significant interactions were seen, categories for several variables revealed contrasting overall associations and/or clear dose-response (Fig 3). For premenopausal women, these included women with BMI > 25 , those who had breastfed, those who were not current smokers, and those who consumed more than 2.32 G of alcohol per day. In addition, the association was stronger

for both pre- and postmenopausal women who were least likely to have genetic basis for their ovarian cancer, defined as women with no personal history of breast cancer without a primary relative with either ovarian cancer or premenopausal breast cancer, and non-Jewish women (Table 1; <http://links.lww.com/EDE/B2>). No important interactions were observed for postmenopausal women, except for weight and BMI, HT use, and the combined "genetic" variable.

Table 4 shows ORs stratified by menopausal status and histologic subtype of epithelial ovarian cancer. Overall, talc use increased risk for serous and endometrioid invasive and serous borderline tumors with the dose-response most apparent for serous invasive cancer. For premenopausal women, both the overall associations and dose-responses were stronger with serous invasive and serous borderline tumors. Premenopausal women also had an increased risk for mucinous borderline tumors at the highest quartile of talc use OR = 2.28 (1.23, 4.26) and a dose-response. For postmenopausal women, dose-responses were stronger for women with invasive serous and endometrioid tumors. Talc use was not associated with clear cell or mucinous invasive epithelial ovarian cancer regardless of menopausal status. The ORs and dose-responses for the combined histologic subtypes relevant to pre- and postmenopausal women are shown in Table 5. Except for a few categories, these were not materially different than those illustrated in Figure 2. However, notably, premenopausal women and postmenopausal HT-users with the relevant subtypes who had accumulated > 24 talc-years had ORs (95% CI) of 2.33 (1.32, 4.12) and 2.57 (1.51, 4.36), respectively.

TABLE 3. Effect of Tubal Ligation and Hysterectomy by Menopausal Status and Hormone Therapy on Association Between Genital Talc Use and Ovarian Cancer

Genital Talc Use Among Women Who Had a Hysterectomy or Tubal Ligation ^a	Premenopausal			Postmenopausal, Never Used HT			Postmenopausal, Ever Used HT		
	Controls	Cases	Adjusted ^b	Controls	Cases	Adjusted ^b	Controls	Cases	Adjusted ^b
	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)
NEVER used	147 (79)	94 (71)	1.00 (REFERENCE)	139 (67)	113 (67)	1.00 (REFERENCE)	130 (77)	58 (48)	1.00 (REFERENCE)
Used BOTH before AND AFTER	26 (14)	17 (13)	0.99 (0.48, 2.06)	45 (22)	36 (21)	1.00 (0.58, 1.72)	21 (13)	40 (33)	5.85 (2.88, 11.9)
Used before ONLY	10 (5)	20 (15)	4.40 (1.73, 11.2)	20 (10)	16 (10)	0.99 (0.46, 2.10)	12 (7)	18 (15)	3.49 (1.39, 8.75)
Used AFTER ONLY	3 (2)	1 (1)	0.33 (0.03, 3.60)	3 (1)	4 (2)	1.66 (0.34, 8.21)	5 (3)	5 (4)	2.11 (0.49, 9.17)

^aThe median ages for tubal ligation and hysterectomy, respectively, were 34 and 39 for cases and 34 and 40 for controls.

^bAdjusted for REFERENCE AGE (CONTINUOUS), study CENTER study phase (3, 4, 5), parity (Nulliparous, 1, 2, ≥2), breastfeeding (NEVER <4, 4–9, 10–19, >19 months), OC use (NEVER <23, 23–49, 50–96, >96 months), IUD (NEVER EVER, Endometrios or RPA/NuLpRods, perONALhSty of bREASTCANCER Jewish ETHNICITY, tubALIGAtION AND BMI (<22.2, 22.2–24.8, 24.9–28.6, >28.6).

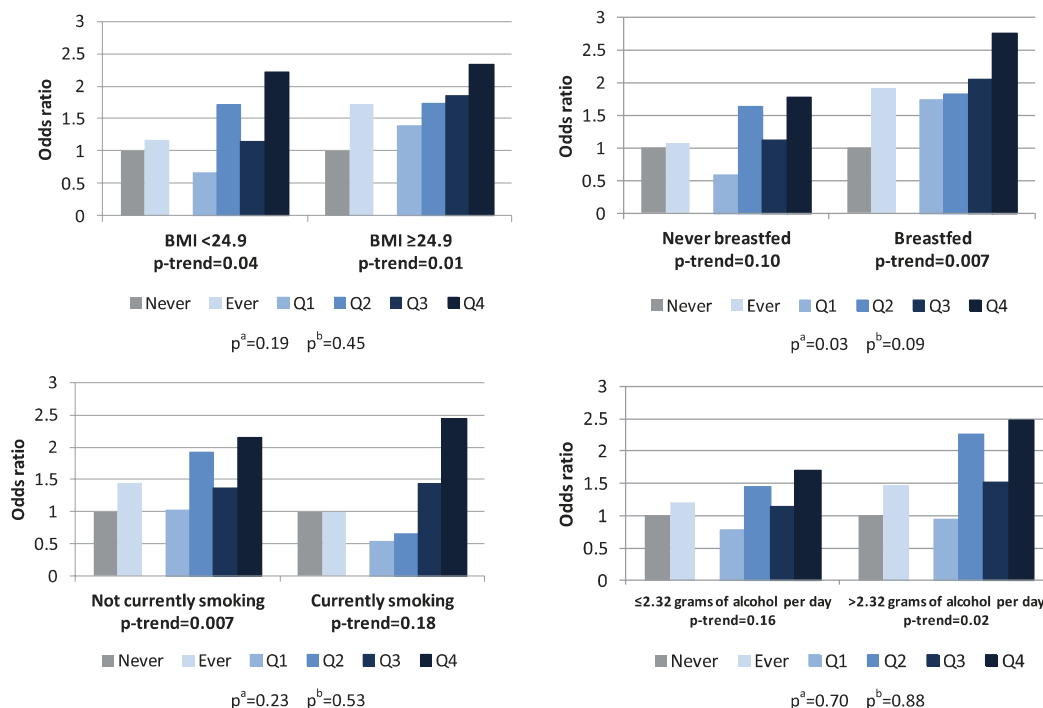


FIGURE 3. Variables modifying the talc association in premenopausal women. ^aP heterogeneity from likelihood ratio tests comparing a model with ever/never talc use and the effect modifier to a model with these plus the interaction term between them. ^bP heterogeneity from likelihood ratio tests comparing a model with indicators for each quartile of talc-years and the effect modifier to a model with these plus their interaction terms.

DISCUSSION

WE ANALYZED CASE-CONTROL DATA COLLECTED OVER 16 YEARS ON TALC USE AND EPITHELIAL OVARIAN CANCER RISK TO ADDRESS ISSUES RELATED TO DEFINITION OF THE EXPOSURE, BIAS AND CONFOUNDING, EFFECT MODIFICATION, HISTOLOGIC HETEROGENEITY, AND DOSE-RESPONSE. TALC USE REGULARLY IN THE GENITAL AREA WAS ASSOCIATED WITH A 33% INCREASE IN OVARIAN CANCER RISK OVERALL WHILE NO APPARENT RISK WAS ASSOCIATED WITH TALC USE ONLY IN NON-GENITAL AREAS. OUR RESULTS ARE CONSISTENT WITH A RECENT POOLED ANALYSIS FROM THE OCAC WHICH REPORTED THAT USE OF POWDER ON GENITALS

IS ASSOCIATED WITH A 24% INCREASED RISK AND NO EFFECT OF NON-GENITAL USE OF TALC.¹⁹ THERE WAS GENERAL AGREEMENT ON RISK BY HISTOLOGIC TYPE OF EPITHELIAL OVARIAN CANCER EXCEPT THAT OCAC FOUND AN ASSOCIATION WITH CLEAR CELL CANCER AND WE DID NOT. THE FINDINGS FROM OCAC AND OUR STUDY CONTRAST WITH NULL RESULTS FROM THE WHI COHORT ANALYSIS¹⁷ RAISING THE ISSUE OF RECALL BIAS IN CASE-CONTROL STUDIES.

ADDRESSING RECALL BIAS, WE CONDUCTED A SENSITIVITY ANALYSIS THAT ASSUMED TRULY NON-EXPOSED CASES AND CONTROLS WERE ACCURATELY CLASSIFIED AS UNEXPOSED (I.E., SPECIFICITY 99%) AND

^aAdjusted for REFERENCE AGE (CONTINUOUS), STUDY CENTER, STUDY PHASE (3, 4, 5), PARTY (Nulliparous, 1, 2, ≥2), BREASTFEEDING (NEVER <4, 4-9, 10-19, >19 months), OC USE (NEVER <23, 23-49, 50-96, >96 months), HT USE (pRimenopAusA₁, postMenopAusALNzERusted, postMenopAusALusEd HT), IUD (NEVER EVER, ENDOMETRIOSIS OR PAINFUL PERIODS, PEROMENORRHEA OF BREATHCANCER, JEWISH ETHNICITY, TUBALIGATION AND BMI (<22.2, 22.2-24.8, 24.9-28.6, ≥28.6)).

TABLE 5. Associations Between Genital Talc Use (Never/Ever and Quartiles of Talc-years) and Ovarian Cancer by Menopausal Status and Postmenopausal Hormone Therapy Among Restricted Histologic Types

Genital Talc Use	Premenopausal			Postmenopausal, Never Used HT			Postmenopausal, Ever Used HT		
	Controls	Cases ^a	Adjusted ^b	Controls	Cases ^a	Adjusted ^b	Controls	Cases ^a	Adjusted ^b
	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)
NEVER	735 (79)	531 (72)	1.00 (REFERENCE)	507 (69)	378 (69)	1.00 (REFERENCE)	309 (72)	152 (53)	1.00 (REFERENCE)
Ever	197 (21)	211 (28)	1.42 (1.12, 1.81)	230 (31)	173 (31)	1.00 (0.78, 1.28)	122 (28)	133 (47)	2.32 (1.64, 3.27)
No GENITAL use	735 (79)	531 (72)	1.00 (REFERENCE)	507 (69)	378 (69)	1.00 (REFERENCE)	309 (72)	152 (54)	1.00 (REFERENCE)
≤1	70 (8)	47 (6)	0.90 (0.60, 1.37)	40 (6)	36 (7)	1.32 (0.80, 2.17)	28 (7)	28 (10)	2.02 (1.10, 3.70)
>1–5	44 (5)	52 (7)	1.66 (1.06, 2.60)	52 (7)	32 (6)	0.81 (0.50, 1.32)	28 (7)	29 (10)	2.56 (1.40, 4.67)
>5–24	59 (6)	68 (9)	1.54 (1.04, 2.28)	61 (8)	41 (8)	0.86 (0.55, 1.33)	26 (6)	30 (11)	2.18 (1.19, 4.00)
>24	21 (2)	41 (6)	2.33 (1.32, 4.12)	70 (10)	56 (10)	1.00 (0.68, 1.49)	36 (8)	43 (15)	2.57 (1.51, 4.36)
P TREND			0.0006			0.88			0.001

^aPostmenopausal Cases ARE TRICED To sERus AND EndometRIoid INvAsIVE, pREMenopAusAL Cases AdDITIoNALLY INClude sERous AND mucINous boRIERINE Cases.

^bAdjusted for REFERENCE AGE (CONTINuous), sTudy GENER sTudy phASE (3, 4, 5), pARTY (NullIpARus, 1, 2, ≥2), BREASTFEEDING (NEVER <4, 4–9, 10–19, >19 moNths), OC use (NEVER <23, 23–49, 50–96, >96 moNths), IUD (NEVER Ever), EndometRIosIs oRpANULepHos, pERoNAlhIsTICy of BREASTCANCER, JEWish ETHNICITy, TAbAlIGATIoN AND BMI (<22.2, 22.2–24.8, 24.9–28.6, >28.6).

Truly Exposed Cases were Also CORRECTly CLASSIFIED (sENSITIVITy 99%). The OR of 1.33 IN our sTudy would bE Nullified If the sENSITIVITy of CORRECTly CLASSIFIED CoNTROls FELT bE 82% oR 18% mIsCLASSIFICATION UNFORtUNATelY, THERE ARE No EXTERNAL RECoRds To vAlIDATE TAlC use REPoRTed by sTudy pARTICIPANts To AssEss whETHER this DEGREE of mIsCLASSIFICATION Is REASONAbLE. SomEwhAT ANALoGous To TAlC AND ovARIAN CANCER Is AlCoHoL use AND BREASTCANCER NuRSEs' HEAlth STudy INvESTIGAToRs EXAMINED THE LATER ASSOCIATION bOTH WITH pROSPECTIVE DATA CoLLECTED AT bASElINE AND RETROSPECTIVE DATA oBTAINED by RESURvEYING subJECts AFTER dIAGNosis.²⁵ They found AN (AGE Adjusted) OR for BREASTCANCER of 1.42 ASSOCIATED WITH 30 oR MORE GRAMS of AlCoHoL dAY RELATIVE To NoNDINKERS fRoM THE pROSPECTIVE DATA COMPARED WITH 1.33 fRoM THE RETROSPECTIVE DATA. This CHANGE bETWEEN Two ANALysEs would oCCUR If THE sENSITIVITy of CoNTROls CORRECTly RECALLING AlCoHoL use dROPPed To 91% (oR 9% mIsCLASSIFICATION). This sUGGESTs somE DEGREE of mIsCLASSIFICATION IN RETROSPECTIVE DATA bUT NoT AS GREAT AS THE 18% REQuired To Nullify THE ASSOCIATION bETWEEN use of TAlC oN GENITALs AND ovARIAN CANCER RIsK IN our sTudy. No COMPARABLE sTudy oN TAlC COMPARING RESuLTs fRoM pROSPECTIVE vERSus RETROSPECTIVE DATA hAs BEEN pERFoRmed. HowEvER, sEVERAL oBSERVATIons ARE INCOMPATIBLE WITH THE POSSIBIlITy THAT RECALL bIAS EXPLAINS THE ASSOCIATION (1) ORs ARE GENERALLY LoWER IN sTudIES whIch AskEd About "Ever use" of TAlC^{8,11} COMPARED WITH Those THAT sPECIFIED REGULAR use^{6,7,9,12,13} wHEREAs hIGHER ORs would bE EXPECTEd If Cases ARE MORE lIkElY To RECALL limited Ever use; (2) No ASSOCIATION WITH NoN GENITAL TAlC use; (3) RIsK vAREs by hIsToLoGIC TyPe; (4) THE ASSOCIATION Is sTRONGER IN pREMenopAusAL women who ARE CloSER IN TIME To TAlC use AND lESS lIkElY To hAVE foRGoTTEnit; AND (5) ORs fRoM RECENT sTudIES^{11,13} ARE LoWER THAN Those fRoM EARLIER oNEs,^{6,7} wHEREAs INCREASING publicITy About THE ASSOCIATION vERy RECENTlY hEAD To GREATER RECALL bIAS AND hIGHER ORs IN MORE RECENT sTudIES. RELATED

ARGUMENTS THAT Cases INITIATE TAlC use bECAUSE of TREATMENT of ovARIAN CANCER oR EARly symPToms of dIsEASE Also LACK mERT bECAUSE WE CENSoRED EXPosuREs 1 yEAR bEFORE THE dATE of dIAGNosis AND most TAlC users bEGAN THE hABIT ARoUND AGE 20—A dECADe oR MORE bEFORE THE ovARIAN CANCER dIAGNosis.

WhETHER THE ASSOCIATION Is A RESuLT of CoNFoUNDING musT Also bE AdRESSed. A 1998 ARTIClE IDENTIFIED BMI, smOKING AND AlCoHoL use As poTENTIAL CoRRelATES of TAlC use IN THE GENERAL popuLATION.²⁶ IN our sTudy, powDER users wERE MORE lIkElY To bE oLDER, fRoM MORE uRBAN subuRBAN AREAs, hEAVIER, As THEMAs sUFFERERS, AND REGULAR ANGESICs users. HowEvER, NoNE of THESE oR oTHER TABLE 2 vARIABLES ALTERED THE ovERALL ASSOCIATION by MORE THAN 10%, pROvIDING No INDICATION of CoNFoUNDING TAlC use wAs Also GREATER IN AfRICAN AMERICANS AND NoTABly ASSOCIATED WITH AhIGH, AlBEIT IMPRECISE, OR (AND 95% CI) of 5.08 (1.32, 19.6). This FINDING CLEARly REQUIRES fURTHER sTudy.

THE oBSERVATION THAT TAlC users, bOTH Case AND CoNTROL subJECts, wERE MORE lIkElY To sAY They hAd As THEMAs NoT bEEN pREvIoUsly REPoRTed. THE lINK bETWEEN powDER use AND As THEMAs mAY NoT bE fully APPRECIATED fRoM TABLE 2 sINCE women who used TAlC As A body powDER bUT NoT To THE GENITAL AREA wERE CLASSIFIED As NoN EXposed. MAKING No body oRGANAL EXPosuRE THE NoN EXposed REFERENCE Group AND As THEMAs THE ouTCOME, THE ORs (AND 95% CI) foR As THEMAs foR body EXPosuRE To TAlC Is 1.27 (0.80, 2.03) foR Cases AND 1.02 (0.66, 1.57) foR CoNTROls. THE COMPARABLE OR foR GENITAL use of TAlC WITH oR wITHoUT body use Is 1.48 (1.00, 2.18) foR Cases AND 1.45 (1.00, 2.10) foR CoNTROls. SIXTy of 85 Cases (70%) WITH As THEMAs AND 57 of 89 (64%) CoNTROls REPoRTed THAT TAlC use pREDATED As THEMAs oN sET AlThOUGH CHANCE musT bE CoNSIDEREd A POSSIBlE EXPLANATION foR THIS NoVEL FINDING, TAlC Is A CAUSE of oCCUpATIOnAL As THEMAs⁷ AND RESPIRABly dIsTRESS hAs bEEN REPoRTed IN INFANts AFTER TAlC wAs ACCIDENTALLY INhAlED.²⁸ THAT As THEMAs mAY bE ASSOCIATED WITH use of TAlC Is IMPoRTANT NoT oNly bECAUSE of HEAlth

CONSEQUENCES ON THE OWN BUT ALSO BECAUSE IT MAY SHED LIGHT ON BIOLOGIC MECHANISMS POTENTIALLY RELEVANT TO THE Talc AND Ovarian Cancer Association.

ALTHOUGH WE FOUND NO EVIDENCE OF CONFOUNDING, WE DID FIND SEVERAL EXAMPLES OF EFFECT MODIFICATION OF THE ASSOCIATION BETWEEN Talc AND Epithelial Ovarian Cancer. OVERALL, THE ASSOCIATION WAS GREATER IN WOMEN WITH NO PERSONAL HISTORY OF BREAST CANCER, THOSE WHO HAD A TUBAL LIGATION OR Hysterectomy, IN PREMENOPAUSAL WOMEN, AND POSTMENOPAUSAL WOMEN WHO HAD USED HT. AMONG THESE FACTORS, PERHAPS THE MOST IMPORTANT IS EFFECT MODIFICATION OF THE ASSOCIATION BY MENOPAUSAL STATUS AND MENOPAUSAL HT.

APPARENT LACK OF AN ELEVATED RISK FOR Epithelial Ovarian Cancer FROM Talc USE IN POSTMENOPAUSAL WOMEN WITHOUT HT USE HAS NOT BEEN REPORTED PREVIOUSLY. EXPLANATIONS MIGHT INCLUDE THAT THERE IS NO ASSOCIATION WITH Talc USE IN THE ABSENCE OF ENDOGENOUS OR EXOGENOUS ESTROGEN, FADING MEMORY OF PAST EXPOSURES, WOMEN WHO WILL DEVELOP Ovarian Cancer FROM Talc USE LEAVE THE AT-RISK POOL BEFORE THEY REACH MENOPAUSE, OR MORE COMPLEX INTERACTIONS WITH MULTIPLE RISK FACTORS AND GENE-ENVIRONMENT INTERACTIONS. OF POSSIBLE RELEVANCE, MOORMAN ET AL.²⁹ OBSERVED THAT REPRODUCTIVE EVENTS THAT CLEARLY AFFECT RISK IN PREMENOPAUSAL WOMEN MAY NOT AFFECT RISK TO THE SAME DEGREE IN POSTMENOPAUSAL WOMEN. WHATEVER THE EXPLANATION, OUR OBSERVATION CHALLENGES THE RELEVANCE OF THE WHI STUDY TO THE Ovarian Cancer Talc ASSOCIATION SINCE ONLY POSTMENOPAUSAL WOMEN WERE ENROLLED IN WHI AND HT USE WAS EXAMINED ONLY AS A COFOUNDING, NOT AN EFFECT MODIFIER.¹⁶ FURTHER STUDY WILL BE NECESSARY TO CLARIFY THE ROLE THAT Talc MAY PLAY IN POSTMENOPAUSAL WOMEN WHO DID NOT USE HT WITH A FOCUS ON THOSE FACTORS THAT MAY INCREASE ENDOGENOUS ESTROGEN, SUCH AS GREATER BMI.

THAT THE ASSOCIATION IS MORE APPARENT IN PREMENOPAUSAL WOMEN AND IN POSTMENOPAUSAL WOMEN WHO USED HORMONAL THERAPY SUGGESTS THAT ESTROGEN PLAYS A ROLE IN THE ASSOCIATION. IN Talc INHALATION STUDIES CONDUCTED BY THE NATIONAL TOXICOLOGY PROGRAM, ONLY FEMALE RATS DEVELOPED LUNG TUMORS.³⁰ LITERATURE ON AIRWAY INFLAMMATION FROM PARTICULATES IS ALSO RELEVANT CITING EVIDENCE THAT AS THAMAMAY BE EXACERBATED DURING PREGNANCY, ZHANG ET AL.³¹ POSTULATED THIS MAY BE DUE TO AN EFFECT OF ESTROGEN ON MACROPHAGE ACTIVITY AND INFLAMMATORY RESPONSE TO PARTICULATES. NORMALLY CONSIDERED INERT, LIKE TITANIUM DIOXIDE (TiO₂), THEIR INVOLVEMENTS DEMONSTRATED THAT MACROPHAGES FROM PREGNANT MICE TRANSPLANTED TO NONPREGNANT RECIPIENTS CONFERRED AN INFLAMMATORY PHENOTYPE IN RESPONSE TO TiO₂. SUCH STUDIES SHOULD BE REPEATED WITH Talc, ANOTHER PARTICULATE CONSIDERED "INERT."

AN EXPLORATORY ANALYSIS OF OTHER POTENTIAL EFFECT MODIFIERS LED TO SEVERAL OTHER OBSERVATIONS THAT MAY HAVE BIOLOGIC RELEVANCE. THE OVERALL ASSOCIATIONS AND DOSE-RESPONSES WERE "STRONGER" FOR PREMENOPAUSAL WOMEN WHO HAD A GREATER BMI, HAD BREASTED, WERE NOT CURRENT SMOKERS, AND CONSUMED ALCOHOL (FIG 3). DUE TO THE LARGE NUMBER OF ASSOCIATIONS TESTED, CHANCE MUST BE THE FIRST EXPLANATION CONSIDERED. HOWEVER,

A COMMON DENOMINATOR COULD BE Prolactin SINCE ITS LEVELS ARE HIGHER IN WOMEN WHO HAVE GREATER BMI,³² BREASTED,³³ DO NOT CURRENTLY SMOKE,³⁴ CONSUME ALCOHOL,³⁵ AND ARE POSTMENOPAUSAL AND USE HT.³⁶ LIKE ESTROGEN, Prolactin MAY HAVE MULTIPLE EFFECTS ON IMMUNE CELLS, ESPECIALLY MONOCYTES AND MACROPHAGES³⁷ WHOSE ROLE IN SCVENGING Talc IN TISSUE IS DEBATED.³⁸ THESE OBSERVATIONS PROVIDE A FRAMEWORK FOR Talc CARCINOGENICITY IN EOC INVOLVING CHRONIC INFLAMMATION.⁹

BIOLOGIC CREDIBILITY OF THE Talc/EOC ASSOCIATION IS ENHANCED BY PERSUASIVE EVIDENCE THAT INERT PARTICLES THE SIZE OF Talc, PRESENT IN THE VAGINA, CAN MIGRATE TO THE UPPERCENTRAL TRACT IN A TECHNIQUE CALLED hysterosalpingoculnography, TECHNETIUM-LABELED ALBUMEN MICROSPHERES ARE PLACED IN THE VAGINA AND THEIR MIGRATION TO THE UPPER TRACT WAS CONFIRMED USING SERIAL SCINTEGRAMS.³⁹ THE MICROSPHERES ARE 5 TO 40 μ m IN DIAMETER—A RANGE WHICH INCLUDES THE SIZE OF SPERM AND Talc. MIGRATION FROM THE VAGINA IS THE OBVIOUS EXPLANATION FOR WHY Talc CAN BE FOUND IN DISEASED (AND SOME NORMAL) OVARIES.³ UNFORTUNATELY, NO EPIDEMIOLOGIC STUDY OF Epithelial Ovarian Cancer AND Talc HAS TAKEN THE OPPORTUNITY TO DETERMINE WHETHER Talc CAN ACTUALLY BE FOUND IN TISSUES REMOVED AT SURGERY AND CORRELATED WITH EXPOSURE TO Talc. A DUE TO Talc's PRESENCE IS BIREFRINGENT PARTICLES FOUND WHEN SLIDES ARE EXAMINED UNDER POLARIZED-LIGHT MICROSCOPY. ALTHOUGH CONFIRMATION THAT THE MATERIALS ACTUALLY Talc REQUIRES SCANNING ELECTRON MICROSCOPY AND X-RAY DISPERSION SPECTROSCOPY, PRESENCE OF BIREFRINGENCE IS A PRACTICAL SCREENING TECHNIQUE AS ILLUSTRATED BY A CASE REPORT OF A WOMAN WITH Ovarian Cancer AND LONG-TERM Talc USE WHO HAD Talc IN HER PELVIC LYMPH NODES FIRST SUGGESTED BY BIREFRINGENCE.⁴⁰

THERE ARE INHERENT LIMITATIONS QUANTIFYING A DOSE-RESPONSE DUE TO A LACK OF METRICS FOR HOW MUCH Talc IS IN AN "APPLICATION," HOW MUCH ENTERS THE VAGINA, AND HOW MUCH REACHES THE UPPERCENTRAL TRACT WHERE, PRESUMABLY, ANY DELETERIOUS EFFECTS MEDIATE. THIS MAY ACCOUNT FOR THE FAILURE TO IDENTIFY A DOSE-RESPONSE IN MANY PAPERS ON Talc AND Ovarian Cancer. OUR 1999 STUDY⁷ SUGGESTED THAT ADJUSTING TO TAL APPLICATIONS BY WHETHER THE CENTRAL TRACT WAS "OPEN" (I.E., EXCLUDING USE AFTER A TUBAL LIGATION OR Hysterectomy AND EXAMINING USE DURING TIMES WHEN OVULATION WAS OCCURRING) YIELDED SIGNIFICANT DOSE-RESPONSES. MILLS ET AL.¹⁰ FOUND A DOSE-RESPONSE BY FREQUENCY OF USE. WU ET AL.,¹² LOOKING AT ALL TYPES OF BODY USE, FOUND A DOSE-RESPONSE WITH ESTIMATED APPLICATIONS. MERRITT ET AL.¹¹ REPORTED A SIGNIFICANT TREND IN RISK FOR INVASIVE SEROUS Ovarian Cancer WITH YEARS OF Talc USE. THE RECENT OCAC ANALYSIS REPORTED NO TREND WITH INCREASING LIFETIME APPLICATIONS *when restricted to talc users*.¹⁹ HOWEVER, AN INCREASE IN RISK WITH INCREASING APPLICATIONS WAS FOUND FOR NONMUCINOUS Epithelial Ovarian Cancer *when nonusers were included*. VIRTUALLY ALL PAPERS THAT HAVE LOOKED AT DOSE-RESPONSE FOR Talc AND Epithelial Ovarian Cancer RISK HAVE INCLUDED NONUSERS IN THE TREND ANALYSIS. IN OUR ARTICLE, WE CALCULATED Talc-YEARS AND SHOWED THAT OVERALL, THERE IS A SIGNIFICANT TREND FOR Epithelial Ovarian Cancer RISK AND Talc-YEARS WHEN NONUSERS ARE INCLUDED, AND THE

trend is even more apparent in premenopausal women with certain epithelial ovarian cancer subtypes.

In summary, this study on talc and epithelial ovarian cancer has contributed the following perspectives, some new, regarding this association:

- (1) Overall, there is an association between genital talc use and EOC and a significant trend with increasing “talc-years” of use.
- (2) Among many epidemiologic variables, no confounders for the association were identified.
- (3) Talc users, both cases and controls, were more likely to report a medical history of asthma.
- (4) The talc/epithelial ovarian cancer association was largely confined to premenopausal women and postmenopausal women who used HT. Other potential effect modifiers in premenopausal women included BMI, breastfeeding, current smoking, or alcohol use. These observations may suggest a role for estrogen and/or prolactin, both known to affect macrophage function and inflammatory response.
- (5) Histologic subtypes of epithelial ovarian cancer more likely to be associated with talc include serous and mucinous borderline tumors and invasive serous and endometrioid tumors.
- (6) For epithelial ovarian cancer categories based on certain effect modifiers or histologic subtypes, stronger overall associations and dose-responses were observed.
- (7) The association may be stronger in African Americans.

An editorial¹⁷ accompanying the WHI study¹⁶ noted that “several case-control studies have reported associations between talc use and ovarian cancer risk” and “no epidemiologic studies have demonstrated a dose-response” (page 2). We believe these appraisals understate the epidemiologic evidence. There have been dozens of case-control studies and several have, in fact, found a dose-response. The editorial further notes that “it does not seem likely that additional conventional epidemiologic studies will strengthen the evidence for or against talc carcinogenicity” (page 2). We believe the observations made here present a good case for talc carcinogenicity and that reanalyses of existing data from already published studies might provide confirmatory evidence. To encourage consolidation of data, we have provided a copy of the “raw” and derived variables examined in our study to NCI dbGaP (available here: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001034.v1.p1) as well as the SAS and Stata programs used in this analysis (eAppendix 1; <http://links.lww.com/EDE/B2>).

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Exhibit 43

Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)

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Abstract

Background: Epidemiologic studies indicate increased ovarian cancer risk among women who use genital powder, but this has not been thoroughly investigated in African American (AA) women, a group with a high prevalence of use. We evaluate the relationship between use of genital powder and nongenital powder in invasive epithelial ovarian cancer (EOC).

Methods: Subjects are 584 cases and 745 controls enrolled in the African American Cancer Epidemiology Study (AACES), an ongoing, population-based case-control study of EOC in AA women in 11 geographic locations in the United States. AA controls were frequency matched to cases on residence and age. Logistic regression was used to calculate ORs and 95% confidence intervals (CI) for associations between genital and nongenital powder exposure and EOC risk, controlling for potential confounders.

Results: Powder use was common (62.8% of cases and 52.9% of controls). Genital powder was associated with an increased risk of EOC (OR = 1.44; 95% CI, 1.11–1.86) and a dose-response relationship was found for duration of use and number of lifetime applications ($P < 0.05$). Nongenital use was also associated with EOC risk, particularly among non-serous EOC cases (OR = 2.28; 95% CI, 1.39–3.74). An association between powder use and upper respiratory conditions suggests an enhanced inflammatory response may explain the association between body powder and EOC.

Conclusions: In a study of AA women, body powder use was significantly associated with EOC risk.

Impact: The results support that body powder is a modifiable risk factor for EOC among AA women. *Cancer Epidemiol Biomarkers Prev*; 25(10); 1411–7. ©2016 AACR.

See related commentary by Trabert, p. 1369

Introduction

Genital powder use may be a modifiable risk factor for epithelial ovarian cancer (EOC), the most deadly of all gynecologic cancers (1). In 2010, the International Agency for

Research on Cancer (IARC) classified perineal (genital) use of nonasbestos-containing, talc-based body powder as "possibly" carcinogenic to humans (2). Although particles of asbestos have been found in older body powder formulations, particularly prior to 1976 (3), more recent body powder formulations no longer contain asbestos (4, 5). However, the relationship between genital powder use and ovarian cancer appears to persist (6). It has been proposed that talc-containing powders may promote cancer development through local inflammation, increased rates of cell division and DNA repair, increased oxidative stress, and increased cytokine levels (7).

A recent pooled analysis of eight population-based case-control studies demonstrated an elevated OR of 1.24 for the association between genital powder use and EOC (6). Some (7–15) but not all (6, 8, 16) previously published studies of talc and ovarian cancer reported a dose-response relationship with genital powder use for frequency, duration, or number of applications. In addition, some studies reported a stronger association among the most common serous histologic subtype (4, 10, 14, 16, 17) although the pooled analysis did not confirm this finding (6). Only one prospective study (17) found a significant association with ever genital talc use and invasive serous EOC (RR = 1.40; 95% CI, 1.02–1.91), although no overall association with EOC was found. The Women's Health Initiative (WHI; ref. 18) did not detect an association with

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genital talc use and EOC. Neither prospective study found evidence of a dose-response relationship.

Previous studies of genital powder use have included mostly white women. However, two studies reported analyses stratified by race and both found an increased EOC risk among African American (AA) women who used genital talc (14, 15). One study reported a nonsignificant association between one or more years of talc use and risk of ovarian cancer, OR = 1.56, [95% confidence interval (CI), 0.80–3.04] among a small sample of 128 AA EOC cases and 143 AA controls, who were shown to have higher prevalence of talc use compared with whites (14). A second study reported an imprecise but significant association with genital talc use with an OR of 5.08 (95% CI, 1.32–19.6) among a very small sample of 16 cases and 17 controls (15). In this article, we present analyses of the relationship between both genital powder and nongenital powder exposure from the African American Cancer Epidemiology Study (AACES), an ongoing, multicenter case-control study of invasive EOC in AA women.

Materials and Methods

Study population

AACES is an ongoing, population-based, case-control study of invasive EOC in AA women in 11 locations (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Institutional review board approval was obtained from all participating institutions. Methods have been described in detail elsewhere (19). Briefly, cases include AA women 20 to 79 years of age with newly diagnosed EOC. With a goal of enrolling an equal number of cases and controls, controls were AA women identified through random digit dialing, with at least one intact ovary and no history of ovarian cancer, and frequency matched to cases on region of residence and 5-year age categories. Participants complete a baseline telephone interview, which includes detailed questions on demographic characteristics; reproductive, gynecologic, and medical history; hormone therapy (HT) and oral contraceptive (OC) use; cancer family history and lifestyle characteristics including smoking, alcohol consumption, and physical activity. In an effort to obtain information from as many women as possible, a short version of the questionnaire is offered to those who would otherwise refuse to participate in the study. Accrual began in December 2010 and as of August 31, 2015, 593 cases and 750 controls were enrolled. Eligibility for this analysis was restricted to participants for whom data on body powder use and all covariates were available, resulting in a final sample size of 584 cases and 745 controls; of these, 49 cases and 16 controls completed the short questionnaire.

Exposure to body powder and talc

In the baseline interview, participants were asked whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Participants were considered "regular users" if they reported using any of these powders at least one time per month for at least 6 months, and "never users" if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or nongenital areas. Participants were categorized according to their type of

application as nongenital use only, genital use only, or genital and nongenital use. Lifetime number of applications was calculated by multiplying the number of body powder applications per month by the number of months used. Occupational exposure to talc (yes, no) was available only for subjects completing the long baseline survey.

Statistical analysis

The prevalence of demographic characteristics was calculated and *t* tests and χ^2 tests were performed to compare distributions between cases and controls. Because of the relatively small number of women who reported having only used genital powder (43 cases and 44 controls), we merged this exposure category with those who reported use of both nongenital and genital powder, creating an exposure category of "any" genital powder use. Unconditional multivariable logistic regression was performed to calculate ORs and 95% CIs for the associations between body powder exposure ("only" nongenital use, and "any" genital use) and risk of EOC. Body powder exposure was further examined by frequency of use (less than 30 times per month, daily), duration of use categorized as less than the median or the median and greater among the controls (<20 years, ≥20 years), and lifetime number of applications categorized as less than the median or the median and greater among controls (<3,600, ≥3,600 lifetime applications). Trend tests for frequency, duration, and lifetime applications of powder use by route of exposure were conducted separately in two subsamples: only nongenital users plus never users and any genital users plus never users. For each subsample, each of the above variables was entered into a logistic regression as multiple indicator variables representing three levels and two degrees of freedom (i.e., for frequency of use: no exposure, less than daily, daily), adjusting for confounders. Trends were evaluated by statistical tests for the association between frequency/duration/lifetime applications with EOC risk, using Wald tests to simultaneously test the equality of parameter estimates with zero. Because experimental data suggest a relationship between inhaled inert particles and asthma (20), a logistic regression analysis was conducted to determine the association between body powder use and upper respiratory conditions (yes/no), controlling for EOC case/control status.

Covariates included reference age in years (age at diagnosis for cases and age at baseline interview for controls); study site [Alabama, Louisiana, New Jersey, North Carolina, Ohio, South Carolina, Texas, Michigan and Illinois (combined because of sample size and regional similarities), Georgia and Tennessee (combined because of sample size)]; education (high school, some after high school training, college or graduate degree); parity (0, 1, 2, 3+); duration of oral contraceptives (never, <60 months, ≥60 months); history of tubal ligation (yes/no); family history of breast or ovarian cancer in a first-degree relative (yes/no); smoking (ever/never); and body mass index (BMI < 25, 25–29.9, ≥30 kg/m²). Two class action lawsuits were filed in 2014 (21) concerning possible carcinogenic effects of body powder, which may have influenced recall of use. Therefore, year of interview 2014 or later (yes/no) was included as a covariate in the logistic regression models. To assess potential reporting bias, we also examined whether there were differences in prevalence of reported powder use by interview year (before 2014, 2014 and later) for cases and controls as well as whether interview year was an effect modifier of the relationship between powder use and EOC risk.

Analyses by the histologic subtype versus all controls were also conducted and heterogeneity of risk estimates was tested by seemingly unrelated regression (22). Because of the missing data for histology, 48 cases were omitted from these analyses. Through stratified analyses, we also assessed possible effect modification of the association with powder use and ever use of HT among postmenopausal women using logistic regression. Experimental data show that the inflammatory response is enhanced in the presence of estrogen and progesterone and we therefore tested for interaction of the association with body powder use by menopausal status (20). Logistic regression and trend analyses were performed using SAS version 9.4 (SAS Institute).

Results

Descriptive statistics for cases and controls are presented in Table 1. Cases were older than controls and had lower educational achievement. Although this study was designed to match controls to cases by 5-year age group, the difference in the age at diagnosis/age at interview may, in part, be because the study is actively enrolling subjects. However, age ranges of cases (20–79 years) and controls (20–79 years) overlap. Significant differences in the distributions of well-established risk factors, including a shorter duration of oral contraceptive use, and lower prevalence of tubal ligation in cases as compared with controls, were as expected. As expected, parity was lower among cases compared with controls, but the difference was not significant. In addition, cases were more likely to report a family history of breast or ovarian cancer. No significant difference in the median years of use of body powder or occupational exposure of talc in cases compared with controls was observed.

Table 2 shows the results of logistic regression models examining the relationship between any use of body powder (either "only" nongenital powder or "any" genital powder) as well as the use of body powder by type of application: "only" nongenital powder use or "any" genital powder use. Adjusting for potential confounders, we observed a significant positive association between any powder use and EOC (OR = 1.39; 95% CI, 1.10–1.76). The OR for the association with "any" genital powder use was 1.44 (95% CI, 1.11–1.86). An OR of 1.31 (95% CI, 0.95–1.79) for the measure of association between "only" nongenital powder use and EOC was only slightly lower in magnitude compared with the association when "any" genital use was reported, but not statistically different from one another ($P = 0.56$). In 2014 and later, we observed an increase in any powder use of 12% and 6% of cases and controls, respectively. Although increased, these exposure prevalences were not significantly different from those interviewed before 2014 ($P = 0.30$). For those interviewed in 2014 or later, we observed an OR for "any" genital powder use of 2.91 (95% CI, 1.70–4.97) compared with 1.19 (95% CI, 0.87–1.63) before 2014. We observed a weaker OR of 1.26 (95% CI, 0.69–2.32) for 2014 and later compared with 1.40 (95% CI, 0.96–2.03) before 2014 for those who reported "only" nongenital use. A test for effect modification by year of interview was statistically significant ($P = 0.005$).

The ORs for the association between daily use of powder for either "only" nongenital powder use (OR = 1.53; 95% CI, 1.00–2.35) or "any" genital powder use (OR = 1.71; 95% CI, 1.26–2.33) with EOC were larger in magnitude than ORs for less than daily use compared with never use but the test for trend was significant for only "any" genital powder use (Table 2). There is a

Table 1. Characteristics of ovarian cancer cases and controls in the African American Cancer Epidemiology Study (AACES)

	Cases (<i>n</i> = 584) <i>n</i> (%)	Controls (<i>n</i> = 745) <i>n</i> (%)	<i>P</i>
Age (years)			<0.01
<40	31 (5.3)	80 (10.7)	
40–59	299 (51.2)	398 (53.4)	
60+	254 (43.5)	267 (35.8)	
Range (years)	20–79	20–79	
Education			0.02
High school or less	262 (44.9)	278 (37.3)	
Some after high school training	145 (24.8)	210 (28.2)	
College or graduate degree	177 (30.3)	257 (34.5)	
Body mass index (kg/m ²)			0.09
<24.9 (under- and normal weight)	86 (14.7)	140 (18.8)	
25–29.9 (overweight)	148 (25.3)	197 (26.4)	
>30 (obese)	350 (59.9)	408 (54.8)	
Parity (# of live births)			0.06
0	105 (18.0)	96 (12.9)	
1	113 (19.4)	141 (18.9)	
2	136 (23.3)	198 (26.6)	
3+	230 (39.4)	311 (41.6)	
Tubal ligation			0.02
Yes	201 (34.4)	302 (40.5)	
No	383 (65.6)	443 (59.5)	
Oral contraceptive use			<0.01
Never	180 (30.8)	155 (20.8)	
<60 months	230 (39.4)	334 (44.8)	
>60 months	174 (29.8)	256 (34.4)	
First-degree family history of breast or ovarian cancer			<0.01
Yes	149 (25.5)	132 (17.7)	
No	435 (74.5)	613 (82.3)	
Menopausal status			0.31
Premenopausal	158 (27.2)	221 (29.7)	
Postmenopausal	423 (72.8)	522 (70.3)	
Hormone therapy			0.10
Ever use	118 (20.3)	125 (16.8)	
Never use	463 (79.7)	618 (83.2)	
Smoking			0.48
Ever	257 (44.0)	313 (42.0)	
Never	327 (56.0)	432 (58.0)	
Hysterectomy ^a			0.43
Yes	141 (24.1)	166 (22.3)	
No	443 (75.9)	579 (77.7)	
Body powder use (median years) ^b	20	20	0.48
Occupational talc exposure ^c			0.16
Yes	58 (10.8)	62 (8.5)	
No	477 (89.2)	667 (91.5)	
Histologic subtype ^d			
Serous	393 (73.2)		
Mucinous	24 (4.5)		
Endometrioid	72 (13.4)		
Clear cell	13 (2.4)		
Other	35 (6.5)		

^aDefined as hysterectomy 2 years prior to diagnosis for cases and 2 years prior to interview for controls.

^bAmong body powder ever users only.

^cData not available for participants who completed the short questionnaire (49 cases and 16 controls).

^dData missing on histologic subtype for 47 cases.

moderately stronger association for 20 years of "any" genital powder use (OR = 1.51; 95% CI, 1.11–2.06) compared with <20 years of use (OR = 1.33; 95% CI, 0.95–1.86; $P_{\text{trend}} = 0.02$). No dose–response with years of use was detected for "only" nongenital powder use. The ORs for the number of lifetime applications

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Table 2. Adjusted ORs for the associations between mode, frequency, and duration of body powder use and ovarian cancer in the AACES

Exposure	Cases (n = 584) n (%)	Controls (n = 745) n (%)	OR ^a (95% CI)
Body powder use			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Ever use	367 (62.8)	394 (52.9)	1.39 (1.10–1.76)
Body powder use by location			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Only nongenital use	119 (20.4)	140 (18.8)	1.31 (0.95–1.79)
Any genital use	248 (42.5)	254 (34.1)	1.44 (1.11–1.86)
Interview date <2014 (n = 351)		(n = 571)	
Never use	147 (41.9)	286 (48.4)	1.00 (Referent)
Only nongenital use	76 (21.7)	104 (17.6)	1.40 (0.96–2.03)
Any genital use	128 (36.5)	201 (34.0)	1.19 (0.87–1.63)
Interview date >2014 (n = 233)		(n = 154)	
Never use	70 (30.0)	65 (42.2)	1.00 (Referent)
Only nongenital use	43 (18.4)	36 (23.3)	1.26 (0.69–2.32)
Any genital use	120 (51.5)	53 (34.4)	2.91 (1.70–4.97)
Frequency of use			
Never use	217 (37.3)	351 (47.2)	1.00 (Referent)
Only nongenital use			
Less than daily	61 (10.5)	82 (11.0)	1.15 (0.78–1.71)
Daily	58 (10.0)	58 (7.8)	1.53 (1.00–2.35)
<i>P</i> _{trend}			0.09
Any genital use			
Less than daily	88 (15.1)	119 (16.0)	1.12 (0.80–1.58)
Daily	158 (27.2)	134 (18.0)	1.71 (1.26–2.33)
<i>P</i> _{trend}			<0.01
Duration of use			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
<20 years	59 (10.2)	68 (9.2)	1.37 (0.91–2.07)
>20 years	60 (10.3)	70 (9.5)	1.28 (0.85–1.93)
<i>P</i> _{trend}			0.13
Any genital use			
<20 years	101 (17.4)	118 (15.9)	1.33 (0.95–1.86)
>20 years	144 (24.8)	134 (18.1)	1.52 (1.11–2.07)
<i>P</i> _{trend}			0.02
Lifetime body powder applications			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
Below median (<3,600 applications)	60 (10.3)	72 (9.7)	1.35 (0.90–2.03)
Above median (>3,600 applications)	59 (10.2)	66 (8.9)	1.30 (0.86–1.97)
<i>P</i> _{trend}			0.14
Any genital use			
Below median (<3,600 applications)	92 (15.9)	119 (16.1)	1.16 (0.83–1.63)
Above median (>3,600 applications)	152 (26.2)	133 (17.9)	1.67 (1.23–2.26)
<i>P</i> _{trend}			<0.01

^aAdjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

of body powder at or above and below the median support a dose–response with "any" genital powder use ($P_{\text{trend}} < 0.01$) but not for nongenital powder use ($P_{\text{trend}} = 0.14$).

A report of any occupational talc exposure, for those completing the long baseline questionnaire, was found to be positively, but not statistically significantly, associated with EOC (OR = 1.31; 95% CI, 0.88–1.93; data not shown). Table 3 shows an OR of 1.38 (95% CI, 1.03–1.85) for the association in serous cases with "any" genital powder use. Among serous cases, the OR for "only" nongenital powder use was lower in

magnitude and not significant (OR = 1.10; 95% CI, 0.76–1.58). Compared with serous cases, larger and statistically significant ORs are found for the associations with type of powder application in nonserous EOC cases; ORs were 1.63 (95% CI, 1.04–2.55) and 2.28 (95% CI, 1.39–3.74), for "any" genital powder use and "only" nongenital powder use, respectively (Table 3). A comparison of adjusted odds ratios between serous and non-serous histologic subtypes and powder use, detected a difference in "only" nongenital powder use ($P = 0.008$), but did not detect significant differences in association for "any" genital powder use ($P = 0.50$).

The stratified results by menopausal status (Table 4) suggest differences in the association for exposure to "only" nongenital powder use among premenopausal where no association is seen for "only" nongenital powder use, whereas the association with the risk of EOC and "any" genital use is elevated. Among postmenopausal women, we observed positive associations of similar magnitude for both the association between EOC and "only" nongenital powder use (OR = 1.49; 95% CI, 1.04–2.15) and "any" genital powder use (OR = 1.41; CI, 1.03–1.92). However, tests of interaction indicate no evidence for interaction by menopausal status for either route of exposure. Among menopausal women, analyses stratified by HT use suggest a stronger association among users compared with nonusers of HT for both routes of applications, although we detected a borderline, nonsignificant interaction for the associations with "any" genital body powder by HT use ($P = 0.06$). The test for interaction for nongenital body powder by HT use was not significant ($P = 0.76$).

To further consider the underlying mechanism for the relationship between use of body powder and the risk of EOC, we calculated the association between both "only" nongenital powder use and "any" genital powder use and having an upper respiratory condition. Controlling for case–control status, age at diagnosis/interview, study site, education, smoking, and BMI, we found ORs of 1.35 (95% CI, 0.89–2.05) and 1.45 (95% CI, 1.03–2.05) for "only" nongenital and "any" genital powder use, respectively, in relation to a reported respiratory condition, respectively (data not shown). A nonsignificant, but elevated OR of 1.26 (95% CI, 0.77–2.06) was observed with occupational exposure to talc and respiratory conditions (data not shown).

Table 3. Adjusted ORs for the associations between talc use and serous/nonserous EOC

Histologic subtype ^a	Cases n (%)	Controls n (%)	OR ^b (95% CI)
Serous (n = 392)			
Never use	156 (39.8)	351 (47.1)	1.00 (Referent)
Only nongenital use	71 (18.1)	140 (18.8)	1.10 (0.76–1.58)
Any genital use	165 (42.1)	254 (34.1)	1.38 (1.03–1.85)
Nonserous (n = 144)			
Never use	44 (30.6)	351 (47.1)	1.00 (Referent)
Only nongenital use	42 (29.2)	140 (18.8)	2.28 (1.39–3.74)
Any genital use	58 (40.3)	254 (34.1)	1.63 (1.04–2.55)

^aTest for interaction for association with powder use by serous and non-serous histologic subtype and route of body powder exposure was $P = 0.008$ for "only" nongenital powder use and $P = 0.50$ for "any" genital powder use.

^bAdjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

Table 4. Adjusted ORs for the association between EOC risk and body powder by menopausal status and HT use

Exposure	Premenopause			Postmenopause		
	Cases (n = 158) n (%)	Controls (n = 221) n (%)	OR ^a (95% CI)	Cases (n = 423) n (%)	Controls (n = 522) n (%)	OR ^a (95% CI)
Body powder use ^b						
Never use	59 (37.3)	103 (46.6)	1.00 (Referent)	157 (37.1)	247 (47.3)	1.00 (Referent)
Only nongenital use	22 (13.9)	42 (19.0)	0.90 (0.44–1.84)	97 (22.9)	98 (18.8)	1.49 (1.04–2.15)
Any genital use	77 (48.7)	76 (48.7)	1.50 (0.87–2.57)	169 (40.0)	177 (33.9)	1.41 (1.03–1.92)
HT ever/never use ^{c,d,e}						
HT ever use						
Never use				34 (32.1)	55 (48.7)	1.00 (Referent)
Only nongenital use				23 (21.7)	23 (20.4)	1.74 (0.77–3.92)
Any genital use				49 (46.2)	35 (31.0)	2.68 (1.33–5.40)
HT never use						
Never use				122 (38.9)	191 (46.9)	1.00 (Referent)
Only nongenital use				73 (23.3)	75 (18.4)	1.51 (0.99–2.29)
Any genital use				119 (37.9)	141 (34.6)	1.24 (0.87–1.79)

^aAdjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

^bTest for interaction between menopausal status and route of body powder exposure was nonsignificant for only non-genital use ($P = 0.21$) and any genital use ($P = 0.85$) compared with never use.

^cRestricted to postmenopausal women.

^dTest for interaction between HT use and only nongenital use was nonsignificant ($P = 0.76$).

^eTest for interaction between HT use and any genital use was nonsignificant ($P = 0.06$).

Discussion

In the largest EOC case–control study in AA women to date, we observed a positive association between regular use of powder and EOC regardless of the route of application. Users of genital powder were shown to have greater than a 40% increased risk of EOC compared with an increased risk of more than 30% among those who used only nongenital powder. The OR for the association with genital powder use in the current study is consistent with the association reported in AA women by Wu and colleagues (14). Of note, a high proportion of EOC cases (63%) and controls (53%) reported any use of body powder. A dose–response trend was evident for median years of use or greater as well as median number or greater of lifetime applications of "any" genital powder but not for use of "only" nongenital powder. Our results support that the association with "any" genital powder use is similar in premenopausal and postmenopausal women, whereas there appears to be an association with use of "only" nongenital powder use among postmenopausal but not premenopausal women. Associations were found among nonserous EOC cases and among postmenopausal users of HT exposed to either genital or nongenital powder.

Most previous case–control studies have not found an association between nongenital powder use and ovarian cancer, including a large pooled analysis by Terry and colleagues who reported an adjusted OR of 0.98 (95% CI, 0.89–1.07; refs. 6, 16). No prospective studies have evaluated nongenital powder use, nor has any study examined these associations by histologic subtype (17, 18). In the current study, the overall association with nongenital use and EOC was similar to that for genital powder use though it did not reach statistical significance possibly due to small numbers and random variation. However, we also did not find a dose–response relationship with frequency, duration, or lifetime applications of "only" nongenital powder use. Furthermore, we did not detect a significant association with use of "only" nongenital powder among serous cases, whereas the OR for the association with use of "only" nongenital powder showed over a 2-fold signif-

icant increased risk for nonserous EOC. In fact, we found a statistically significant difference between associations by subtype for "only" nongenital use. Given the inconsistency with previous published findings, it is also reasonable that under-reporting genital powder use, such as abdominal powder use that reaches the genital area, may have led to a spurious result. Another possible explanation for our finding may be that there is a higher inflammatory response in AAs compared with whites (23–25). Our results also suggest that the route of powder exposure may have different effects by histologic subtype. As most high-grade serous EOC, but not nonserous subtypes, arise in the fallopian tubes (26), it is possible that direct exposure through the genital tract specifically affects this disease subtype. The association with any genital powder use and nonserous cases may be due to the overlap between genital and nongenital powder use (83% of cases and 83% of controls). We were unable to examine associations with "only" genital powder users due to sample size considerations. In contrast, nongenital powder use may be related to inhalation of the exposure through the lungs. Several large pooled analyses have demonstrated risk factor associations with inflammatory-associated exposures, such as smoking (27), endometriosis (28), and obesity (29) with nonserous histologic subtypes of ovarian cancer but not high-grade serous EOC, providing a plausible theoretical basis for differences we found in associations by histologic subtype.

Akin to talc powders, titanium dioxide (TiO₂) is another inert particle that induces an inflammatory response upon inhalation and has been considered to be "possibly carcinogenic to humans" by IARC (2). Experimental evidence of enhanced inflammation due to exposure to inert environmental particulates of TiO₂ showed inhibition of phagocytic activity of alveolar macrophages in pregnancy, and was found to be associated with increased asthma risk in the offspring of BALB/c mice exposed to TiO₂. In this study, elevated estrogen levels during pregnancy were found to contribute to the resulting asthma risk (20). Our findings also support that enhanced airway inflammation is due to exposure to inert particles.

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Consistent with a recent study (15) where an association with powder use and asthma was reported, the relationship between body powder use and respiratory conditions likely reflects an enhanced inflammatory response due to powder use, suggesting a mechanism by which EOC risk is increased. Therefore, lung inhalation of powder could be a biologically plausible mechanism for the association between nongenital body powder use and increased EOC risk, particularly in nonserous EOC cases.

To further explore whether estrogen influences the inflammatory response, we performed stratified analyses by menopausal status. We did not see a difference in the association with premenopausal compared with postmenopausal use of "any" genital powder use, which is not consistent with a recent report (15) where an association with premenopausal use but not postmenopausal use was found. However, consistent with this report, we found a stronger association between "any" genital powder use and EOC among postmenopausal women who reported HT use compared with nonusers. This finding is also consistent with experimental data showing that in the presence of estrogen and/or estrogen and progesterone, the ability of macrophages to clear inert particulates is altered, enhancing the inflammatory response leading to the development of asthma in mouse offspring (20). It has also been proposed that chronic inflammation, resulting from exposure to body powder, whether through inhalation or through a transvaginal route, may exert a suppressive effect on adaptive immunity, leading to increased risk of EOC (30). These findings suggest that AA women may be particularly susceptible to exposure to body powder due to having higher endogenous estrogen levels compared with white women (31, 32). Because of the limited sample size, we were not able to evaluate associations with the timing or duration of HT use or the concurrent effects of both HT and powder use. Tests for interaction of the associations in the stratified analyses by HT use were not significant and our findings should be considered exploratory.

The results of the current study showed that genital powder use was associated with ovarian cancer risk in AA women and are consistent with localized chronic inflammation in the ovary due to particulates that travel through a direct transvaginal route. The dose-response observed for duration of genital powder use provides further evidence for the relationship between genital powder and overall EOC risk. Our data suggest that the increased risk due to use of genital powder applies to both serous and nonserous histologic subtypes of EOC. Use of "only" nongenital powder was not found to be associated with the serous subtype, but our data suggest a relationship with nonserous EOC. The association with serous EOC is consistent with several previous studies (4, 6, 14–17). Only the pooled analysis found associations with the endometrioid and clear cell subtypes (6). The association with any occupational talc exposure and EOC (OR = 1.31; data not shown), though not statistically significant, is also consistent with the results for "only" nongenital powder use and suggest other routes of exposure, aside transvaginal, may effect EOC risk.

A recent publication of data from the WHI, which did not find an association with genital talc use and ovarian cancer (18), was accompanied by an editorial that emphasized the challenges in assessing the exposure to talc due to the reliance on self-report (33). This limitation in the measurement of the exposure variables in the current study needs to be considered when interpreting our results. The possibility of differential misclassification exists in a

case-control study such as AACES, especially due to heightened awareness of the exposure as a result of two recent class action lawsuits (21). Because of such publicity, we adjusted for date of interview in the analysis. However, there is still a possibility that recall bias may have caused some inflation of the ORs. Although our findings suggest that the publicity of the class action lawsuits may have resulted in increased reporting of body powder use, our data do not support that recall bias alone before 2014 versus 2014 or later would account for the associations with body powder use and EOC. It is possible that the lawsuits sharpened memories of body powder use and improved the accuracy of reported use for both cases and controls interviewed in 2014 or later. As the association with nongenital body powder use is not consistent with the published literature, the possibility of misclassification of exposure, residual confounding, or a chance finding cannot be ruled out as an explanation for the associations with nongenital powder use.

In summary, we found that the application of genital powder is associated with serous and nonserous EOC in AA women, a novel observation in this population that is consistent with some large studies in whites. Our data are consistent with the notion that localized chronic inflammation in the ovary caused by exposure to genital powder contributes to the development of EOC. Although associations with nongenital powder use and EOC have not been previously reported, we cannot rule out the possibility that this relationship may be specific to AA women. The high prevalence of exposure to both genital and nongenital body powder among AA women compared with the mostly white subjects (41%), as in the large pooled analysis (6), underscores the importance of the study's findings. The results of the current study suggest that the use of body powder is an especially important modifiable risk factor for EOC in AA women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.M. Schildkraut, A.J. Alberg, E.V. Bandera, J.S. Barnholtz-Sloan, M.L. Bondy, M.L. Cote, E. Funkhouser, E.S. Peters, A.G. Schwartz, P. Terry, S. Crankshaw, F. Camacho, P.G. Moorman

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.M. Schildkraut, S.E. Abbott, M.L. Bondy, M.L. Cote, L.C. Peres, E.S. Peters, A.G. Schwartz, F. Camacho, F. Wang, P.G. Moorman

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for Cancer Research

Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)

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Exhibit 44



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Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls

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Abstract

Genital powder use has been associated with risk of epithelial ovarian cancer in some, but not all, epidemiologic investigations, possibly reflecting the carcinogenic effects of talc particles found in most of these products. Whether risk increases with number of genital-powder applications and for all histologic types of ovarian cancer also remains uncertain. Therefore, we estimated the association between self-reported genital powder use and epithelial ovarian cancer risk in eight population-based case-control studies. Individual data from each study was collected and harmonized. Lifetime number of genital-powder applications was estimated from duration and frequency of use. Pooled odds ratios were calculated using conditional logistic regression matched on study and age and adjusted for potential confounders. Subtype-specific risks were estimated according to tumor behavior and histology. 8,525 cases and 9,859 controls were included in the analyses. Genital powder use was associated with a modest increased risk of epithelial ovarian cancer (odds ratio 1.24, 95% confidence interval 1.15–1.33) relative to women who never used powder. Risk was elevated for invasive serous (1.20, 1.09–1.32), endometrioid (1.22, 1.04–1.43), and clear cell (1.24, 1.01–1.52) tumors, and for borderline serous tumors (1.46, 1.24–1.72). Among genital powder users, we observed no significant trend ($p=0.17$) in risk with increasing number of lifetime applications (assessed in quartiles). We noted no increase in risk among women who only reported non-genital powder use. In summary, genital powder use is a modifiable exposure associated with small-to-moderate increases in risk of most histologic subtypes of epithelial ovarian cancer.

Keywords

ovarian cancer; powder; talc; epidemiology

INTRODUCTION

Powders that are commonly applied either directly to the genital, perineal, or rectal area after bathing or indirectly to underwear, sanitary napkins, tampons, or stored contraceptive devices may contain talc because of its softness, absorbency, and lack of clumpiness (1). However, the presence of talc in commercially available powder formulations has varied over time, even within particular brands of products, limiting the ability of most epidemiologic studies to measure genital talc exposure accurately. Despite this, genital powder use, but not use on other parts of the body, has been linked to increased risk of ovarian cancer, suggesting that powder particles ascending the genital tract may predispose to ovarian cancer development (2–4). Meta-analyses of observational studies show 33–35% increased risk of ovarian cancer among women who have used genital powders (1, 4, 5), but evidence for a dose-response relationship has been inconsistent. Though dose response was not addressed in previous meta-analyses (1, 4, 5) some individual studies have reported significant dose-response (4, 6–10) while others have not (9, 11–15).

Epidemiologic and biologic studies show differences in risk-factor profiles and molecular characteristics between ovarian cancer subtypes defined by histology (serous, endometrioid, mucinous, clear cell) and behavior (borderline, invasive) (16). For instance, serous tumors are characterized by p53 mutations, while mucinous tumors have a high prevalence of KRAS mutations (17) and are not generally associated with reproductive risk factors (16, 18). Since most early studies of powder use and ovarian cancer did not include analysis by

histologic subgroups (3, 6, 11, 19–21), histology-specific estimates were not available from these studies for meta-analysis. Most (2, 4, 8, 9, 22), but not all (10, 14, 15, 23), epidemiologic studies of genital powder use and risk of ovarian cancer that have evaluated histologic subgroups have found the association to be strongest for serous invasive tumors. Such tumors comprise the most common variety of ovarian cancer and few previous studies have had sufficient statistical power to evaluate the association between genital powder use and risk of other histologic subtypes. In the present study, we evaluated associations between genital powder use and risk of ovarian cancer overall, by invasiveness and by histologic type in a pooled analysis of eight population-based case-control studies with relevant data from the Ovarian Cancer Association Consortium (OCAC), a consortium founded in 2005 to validate promising genetic associations in epidemiologic studies of ovarian cancer.

MATERIALS AND METHODS

Participating studies

Studies participating in the OCAC consortium as of April 2010 that collected data on powder use were included. Each study was approved by an institutional ethics committee and all participants provided informed consent. Detailed description of the OCAC consortium is available elsewhere (24). Characteristics of the eight case-control studies contributing data to this analysis are presented in Table 1. Six studies were conducted in the USA (DOV (14), HAW (25), HOP (26), NCO (27), NEC (4), USC (28)) one study in Australia (AUS (7)) and one study in Canada (SON (15)). Overall, our analyses included 8,525 cases of ovarian, fallopian tube or peritoneal cancer and 9,859 controls. Five studies previously reported on powder use (AUS (7), DOV (14), NCO (27), NEC (4), SON (15)), three of which provided data for this analysis that had not been included in their previous powder-related publication (DOV, NEC, AUS). The remaining three studies have not previously published their genital powder-use data (HAW, HOP, USC).

Exposure and covariate data

Data collected from participants regarding genital powder use varied between studies. Harmonized analytic exposure variables were developed by comparing questionnaires between the eight participating studies. The majority of the studies have obtained information on duration and frequency of powder use, age at first powder use, use by sexual partners, and non-genital use (Table 1). We defined genital powder use as any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, underwear) to the genital, perineal, or rectal area. Since study specific powder questions included varying degrees of detail regarding type and method of application, genital powder definitions differ between studies. Criteria for regular genital powder use varied between studies from “ever use” (AUS) to “one year or longer” (DOV); the specific wording for this question is provided in Table 1. Use of body powders on sites other than the genital area was defined as non-genital powder use. Women who reported both genital and non-genital powder use were classified as genital users. Two studies (DOV, SON) did not collect data on non-genital use and therefore women assigned to “no powder use” for these studies could have a history of non-genital powder exposure. Extensive information on known and suspected risk factors for ovarian cancer was collected in each study, including oral contraceptive (OC) use, parity, tubal ligation history, body mass index (BMI), race, and ethnicity.

Statistical methods

Participants missing case/control status (n=17) or tumor histology (n=19) were excluded from the analysis. We also excluded 1,119 participants who answered “do not know” or

were missing data on genital powder use; most of these were from the NCO study which did not include genital powder questions for the first 720 participants. Furthermore, we excluded participants missing tubal ligation (n=55), OC duration (n=100), parity (n=3), or height or weight (BMI) (n=179). To examine differences in characteristics between cases and controls, we evaluated two-sample t-statistics (age, BMI) and chi square statistics (OC use, nulliparity, tubal ligation, race/ethnicity, powder use).

Study-specific odds ratios (ORs) and 95% confidence intervals (CI) were estimated using unconditional logistic regression and were summarized by forest plots, including study heterogeneity based on Cochran's *Q* statistic. As no significant heterogeneity was observed between studies, we calculated pooled ORs and 95% CIs across the studies using conditional logistic regression matched on 5-year age groups and study. All analyses were adjusted for potential confounders: age (continuous), duration of oral contraceptive (OC) use (never use, use <2yrs, 2–<5yrs, 5–<10yrs, ≥10yrs), parity (0, 1, 2, 3, ≥4 children), tubal ligation history, BMI (quartiles based on distribution in controls), and race/ethnicity (non-Hispanic white, Hispanic white, black, Asian, other). Family history of breast or ovarian cancer were also considered as covariates but were not included in the final model.

Subtype-specific estimates were calculated for subgroups of ovarian cancer defined by behavior (invasive, borderline) and histology (serous, mucinous, endometrioid, clear cell) by comparing each case group to all controls. As borderline endometrioid and clear cell tumors are rare, we did not have sufficient numbers to evaluate those types separately.

In order to measure cumulative dose of genital-powder use, we estimated lifetime number of powder applications by multiplying total months of use by frequency of use per month, for all direct and indirect genital-powder applications. Women who reported multiple types of genital powder exposure (on underwear, on sanitary napkins or pads, directly to genital area) during the same time period were assigned the number of genital powder applications equal to the most commonly used type rather than the sum of applications across all types of genital powder exposure. We reasoned that contemporaneous powder applications were unlikely to be independent events and therefore should not be treated cumulatively.. Analyses of estimated lifetime number of applications excluded participants in the HOP study as data on age and frequency of use were not collected (n=2,224); genital powder users missing information on duration or frequency of use were omitted in the remaining studies (n=394). Never regular users of genital powders and women who only reported non-genital use were coded as having zero lifetime genital powder applications and comprised the reference group for this analysis. Categories were determined based on age-specific quartile cutpoints in controls (25th, 50th and 75th percentile cutpoints are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41–50 years; 720, 3,600, and 10,800 for 51–60 years; 1,440, 5,760, and 14,440 for 61–70; 840, 7,200, and 18,000 for > 70 years). Trends were evaluated based on the median lifetime number of genital-powder applications for controls in each age-specific quartile using the Wald statistic and were performed both including and excluding never users of genital powders.

We estimated the association between genital powder use and ovarian cancer risk within strata to evaluate potential modification of effect defined using a cutpoint BMI of 30 based on the World Health Organization's definition of obesity, endometriosis, parity, tubal ligation/hysterectomy, and menopausal status. We used likelihood-ratio statistics comparing models with and without interaction terms to determine statistically significant interactions. To estimate calendar year of first use, we subtracted the years since first use (age at study entry minus age at first genital powder use) from median calendar year of the participant's study. All analyses were performed in SAS v9.2 (SAS, Cary, NC) and Stata v9.2 (StataCorp,

College Station, TX). All p-values are two-sided. Analyses have been independently verified by two separate study groups (HAW and NCO).

RESULTS

This pooled analysis of eight case-control studies included 9,859 controls and 8,525 ovarian cancer cases. Genital powder use was reported by 2,511 (25%) of the controls and 2,600 (31%) of the cases, while powder use only on other (non-genital) parts of the body was reported by 1,533 (16%) of the controls and 1,282 (15%) of the cases (Table 2). The prevalence of genital powder use in controls varied widely between study sites, highest in AUS (45%) and lowest in HAW (15%, Table 3).

In the pooled analysis, ever regular use of genital powder was associated with a modest increase in risk of ovarian cancer (OR=1.24, 95% CI=1.15–1.33, Table 3) relative to women who reported no powder use (AUS, HAW, HOP, NCO, NEC, USC) or no genital powder use (DOV, SON). We observed no heterogeneity in the risk associated with genital powder use between studies regardless of the reference group ($p=0.61$, Figure 1). Results were similar for genital powder users compared to a combined reference group including never users and women whose use of powder was exclusively non-genital (covariate-adjusted OR=1.25, 95% CI= 1.16–1.34; data not shown), reflecting the absence of an association between powder use on other parts of the body with ovarian cancer risk (Table 3).

Genital powder use was associated with a similar increased risk of borderline and invasive ovarian cancer overall (Table 4). For borderline tumors, the association was stronger for the serous subtype (OR=1.46, 95% CI=1.24–1.72; Table 4) and non-significant for the mucinous subtype. For invasive ovarian cancer, we observed small increases in risk of serous (OR=1.20, 95% CI=1.09–1.32), endometrioid (OR=1.22, 95% CI=1.04–1.43), and clear cell (OR=1.24, 95% CI=1.01–1.52) cancer but no significant increase in risk of mucinous cancer (OR=1.09, 95% CI= 0.84–1.42). Similarly, we observed no significant increase in risk when borderline and invasive mucinous tumors were considered together (data not shown). Risk associated with genital powder use was consistent across studies for borderline and invasive tumors as well as invasive serous, endometrioid, and clear cell subtypes (p for heterogeneity >0.1 ; Figures 2 a,b,c,d,e), but not for mucinous tumors ($p=0.08$; Figure 2f). Genital powder use was associated with increased risk of invasive mucinous tumors in SON, HOP (significantly), and USC (non-significantly) while in the remaining studies (HAW, NCO, AUS, DOV, and NEC) genital powder use was non-significantly associated with reduced risk.

We evaluated cumulative genital-powder exposure as a composite variable of frequency and duration of use. We observed similar increased risks of all non-mucinous subtypes of epithelial ovarian cancer combined across quartiles of genital powder compared to non-use: OR_{Q1}=1.18, 95% CI=1.02–1.36, OR_{Q2}=1.22, 95% CI=1.06–1.41, OR_{Q3}=1.22, 95% CI=1.06–1.40, OR_{Q4}= 1.37, 95% CI=1.19–1.58 (Table 5). Although a significant increase in risk with an increasing number of genital powder applications was found for non-mucinous epithelial ovarian cancer when non-users were included in the analysis (p -trend <0.0001), no trend in cumulative use was evident in analyses restricted to ever-users of genital powder (p -trend=0.17; Table 5). Taken together, these observations suggest that the significant trend test largely reflects the comparison of ever regular use to never use. Since tubal ligation or hysterectomy would block the transport of powder through the genital tract to the ovaries, we performed a sensitivity analysis excluding women who started genital powder use after these procedures. We observed similar associations when we excluded the 65 cases and 79 controls who started genital powder use for the first time after surgery (OR_{Q1}=1.19, 95% CI=1.03–1.38, OR_{Q2}=1.19, 95% CI=1.03–1.38, OR_{Q3}=1.21, 95% CI=1.04–1.39, OR_{Q4}=

1.36, 95% CI=1.18–1.57). For studies that collected data on timing of powder use and tubal ligation/hysterectomy, we were able to identify timing of genital powder exposure in relation to surgery based on age of powder use and age at surgery. Restricting our exposure to genital powder applications that occurred before tubal ligation or hysterectomy made no substantive difference in the results.

The association between any genital-powder use and ovarian cancer risk was stronger among women with BMI < 30 kg/m² (OR=1.28, 95% CI=1.17–1.39) than for women with BMI > 30 (OR=1.14, 95% CI=0.98–1.32, p-interaction=0.01). We observed no significant interactions between genital powder use and parity, reported history of endometriosis, tubal ligation/hysterectomy, or menopausal status (all p-interaction > 0.1). The association between genital powder use and ovarian cancer risk was similar for women who started use between 1952 and 1961 (OR=1.36, 95% CI=1.19–1.56), between 1962 and 1972 (OR=1.27, 95% CI=1.11–1.46), and after 1972 (OR=1.31, 95% CI=1.15–1.51). However, we observed an attenuated association for women who started genital powder use before 1952 (OR=1.08, 95% CI=0.93–1.25).

DISCUSSION

This pooled analysis of eight case-control studies suggests that genital powder use is associated with a modest 20–30% increase in risk of developing epithelial ovarian cancer, including serous, endometrioid, and clear cell tumors, but is less relevant to invasive mucinous tumors. Our findings are consistent with and extend the findings of three meta-analyses that have reported an increased risk of epithelial ovarian cancer with genital-powder use (1, 4, 5) by including dose response and histology specific analyses. Our estimate of the overall association between genital powder use and ovarian cancer risk was slightly attenuated compared to previous estimates from meta-analyses. Possible reasons for the difference include the lack of restriction to published results, data harmonization between studies that allowed similar definitions for the exposure and covariates, and chance. Based on the consistency in the epidemiologic literature on talc-based powder and ovarian cancer risk, the International Agency for Research on Cancer (IARC) classified talc-based body powder as a class 2b carcinogen “possibly carcinogenic to human beings” (29).

The biologic plausibility for the observed association between genital-powder use and ovarian cancer risk has been challenged because evidence for dose-response has been inconsistent (2, 4, 5, 9, 10, 15, 22). The lack of significant dose-response may reflect the difficulty inherent in accurate recollection of specific details of frequency and duration of genital-powder use. Also, because not all powder products contain talc, various products may differ in their potential carcinogenic effects. **Alternatively, the association between genital-powder exposure and ovarian cancer risk may not be linear and a modest exposure may be sufficient to increase cancer risk.** Talc-containing powders are hypothesized to promote cancer development by ascending the female genital tract and interacting directly with the ovarian surface epithelium, leading to local inflammation characterized by increased rates of cell division, DNA repair, oxidative stress, and elevated inflammatory cytokines (13). Particles in solution easily ascend the genital tract (30, 31). Our finding of slightly attenuated associations following exclusion of women with powder exposure after tubal ligation or hysterectomy are not supportive of this hypothesis, but risk estimates in this subgroup analysis may have randomly differed from those including all women because of the reduction in sample size. Talc particles have been observed in the ovaries of humans (32) and in rodent models (33, 34), but little is known about the biologic effects of genital powder use.

In the current analyses of the various histological subtypes of ovarian cancer, we confirmed previous reports of increased risk of serous invasive tumors with genital-powder use (2, 4, 8, 9, 22). We also observed significantly increased risk of both endometrioid and clear cell invasive ovarian tumors with use of genital powder, and this finding was consistent across studies. It has been suggested that both endometrioid and clear cell ovarian tumors may originate from ectopic uterine endometrium (endometriosis) implanted on the ovary (17). In contrast, we observed no significant associations between genital powder use and either borderline or invasive mucinous ovarian cancer. The lack of a significant association for mucinous tumors may be due to the relatively small number of these tumors or could be an indication that powder exposure is not relevant to the pathogenesis of this histologic type. Studies have noted that ovarian cancer risk factors and molecular characteristics differ for mucinous tumors (16–18, 23, 35–39).

Limitations of our pooled analysis include differences in the wording of questions about genital powder use between studies and the retrospective nature of the exposure ascertainment. Women who were classified as genital-powder users varied from “ever” use (AUS) or “ever regular” use (SON) to powder use for at least six months (HAW, HOP, NCO, NEC, USC) or at least one year (DOV). Differences in genital powder questions result in varying levels of misclassification of true genital powder exposure. However, since exposure definitions are the same for cases and controls within each study, misclassification genital powder exposure due to the question wording would be non-differential, leading to an underestimate of the true association for any given study. These studies were retrospective in nature and therefore potentially susceptible to bias if cases were more likely to report genital-powder use than controls. Although non-genital powder use was not associated with ovarian cancer risk, it is nevertheless possible that any overreporting of powder use by cases might have been limited to reporting of genital powder. Our analyses were also limited by missing data on genital powder use; however, missingness was not associated with the distribution of any of the ovarian cancer risk factors examined and was thus not likely to bias our results. Strengths of our analysis include a large sample size and pooled analysis of individual data, allowing evaluation of the association of genital powder use with less common histologic subgroups of ovarian cancer, careful harmonization of the data based on comparison of study questionnaires, the use of a composite variable combining duration and frequency to assess dose-response relationships.

In conclusion, our large pooled analysis of case-control studies shows a small-to-moderate (20–30%) increased risk of ovarian cancer with genital-powder use, most clearly pertaining to non-mucinous epithelial ovarian tumors. More work is needed to understand how genital powders may exert a carcinogenic effect, and which constituents (e.g. talc) may be involved. Since there are few modifiable risk factors for ovarian cancer, avoidance of genital powders may be a possible strategy to reduce ovarian cancer incidence.

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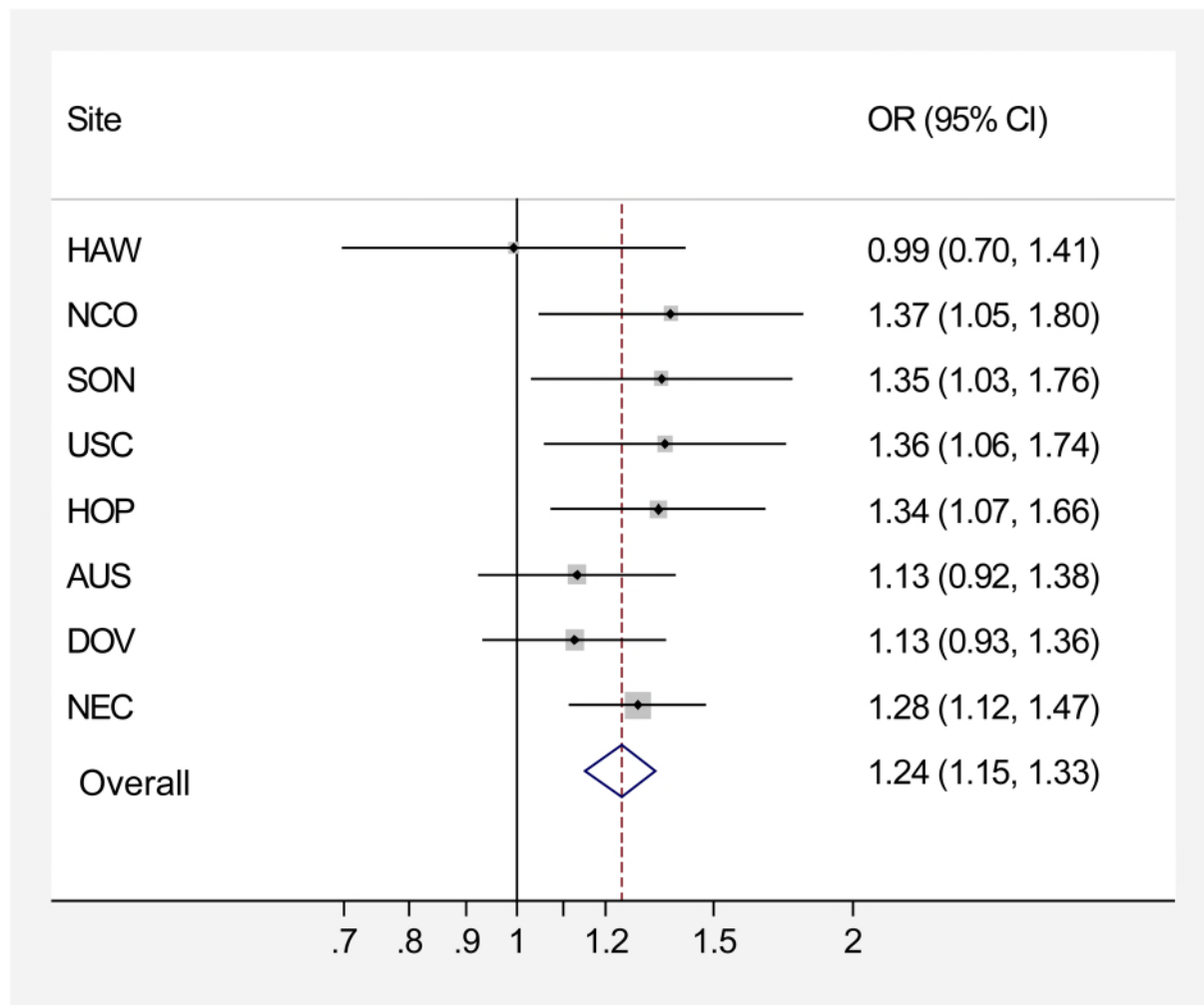
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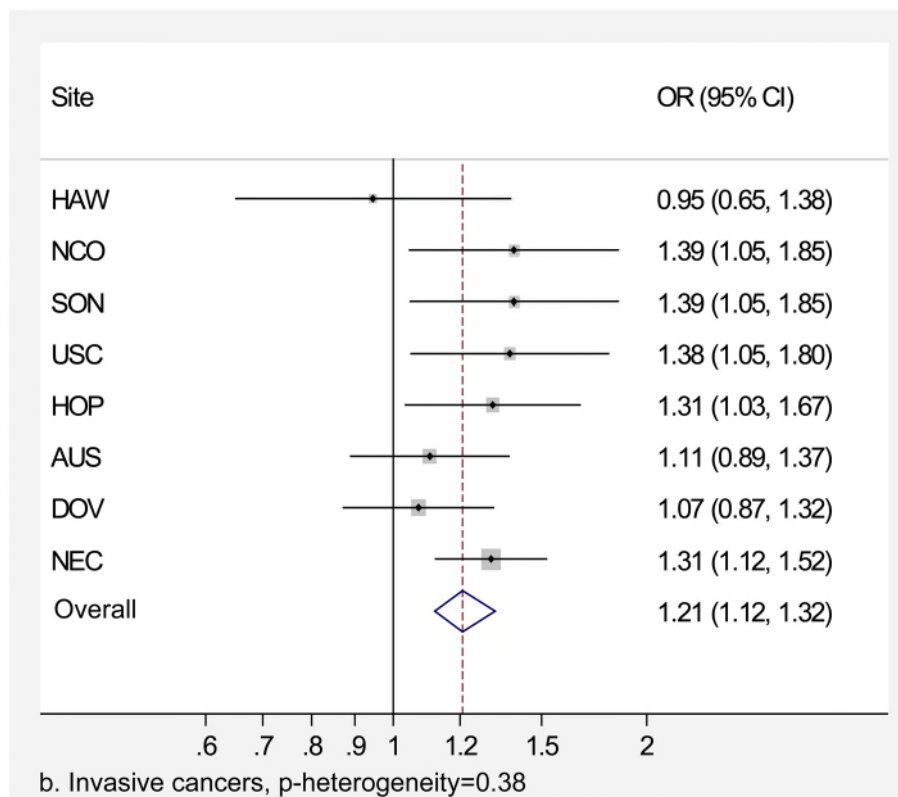
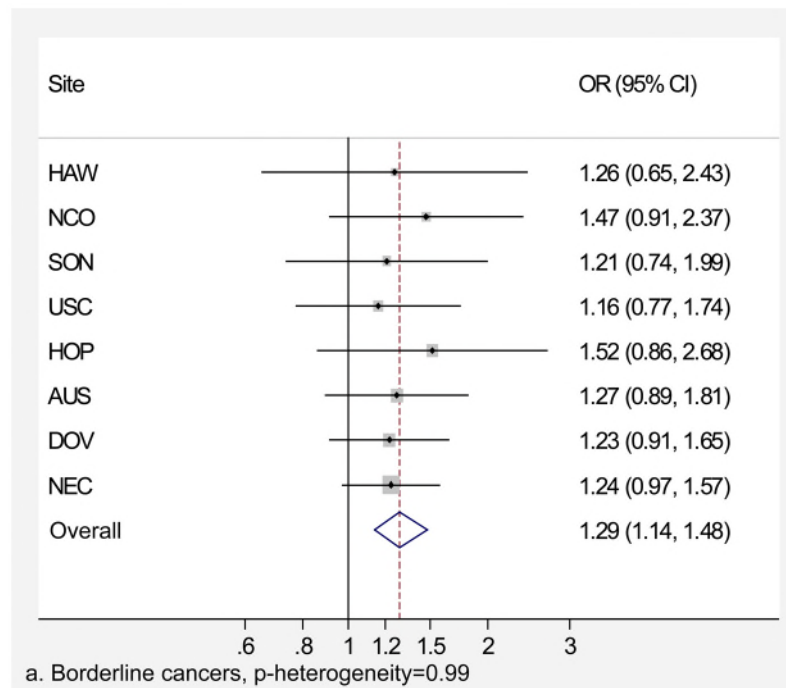
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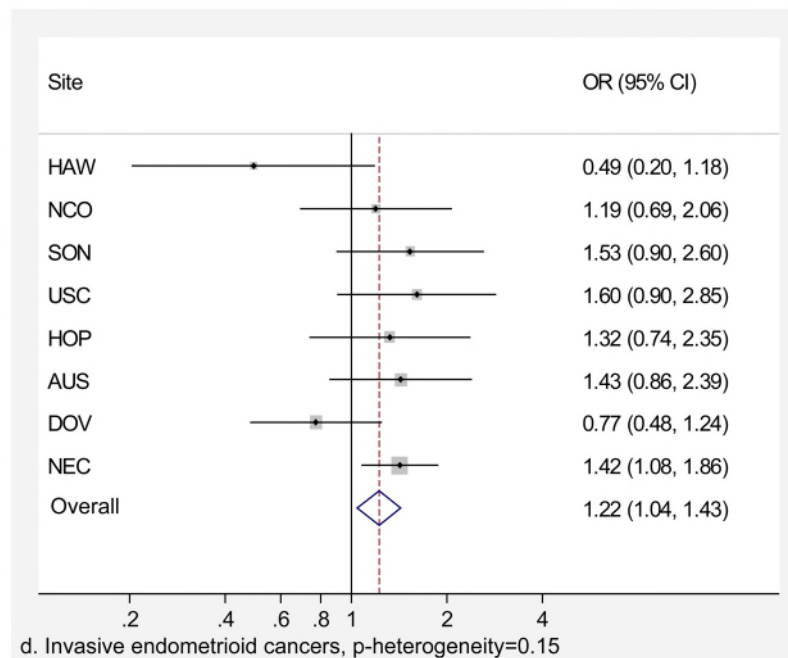
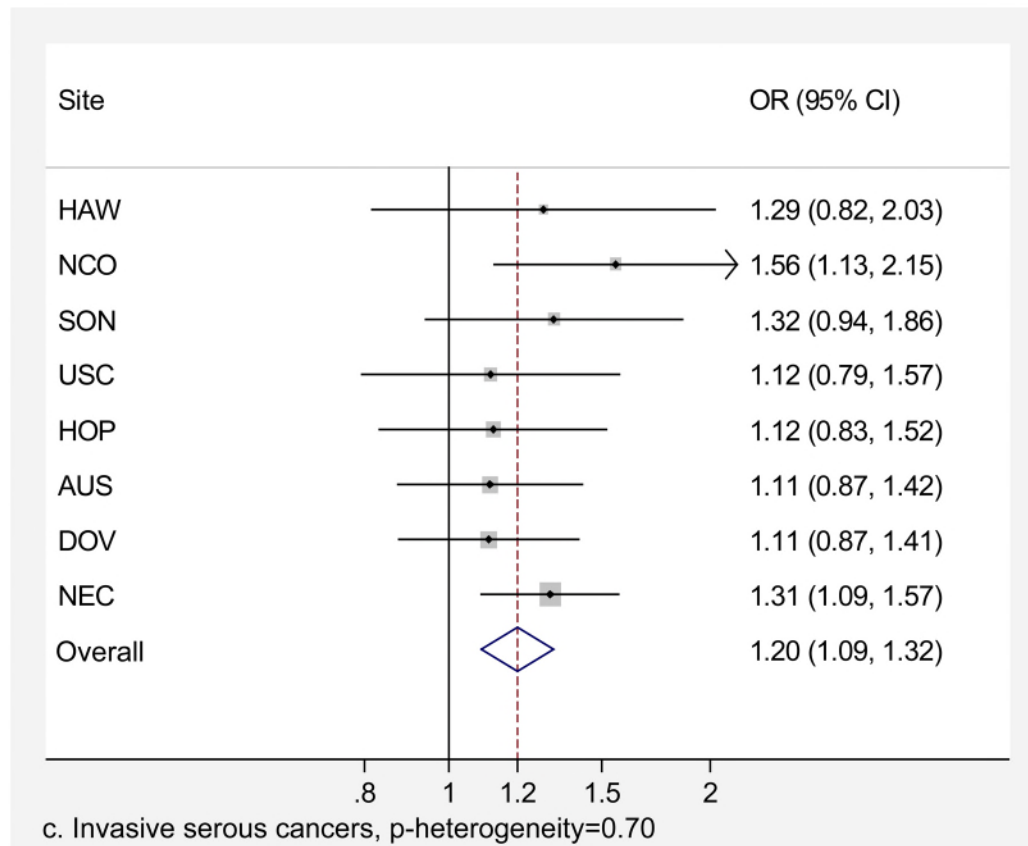
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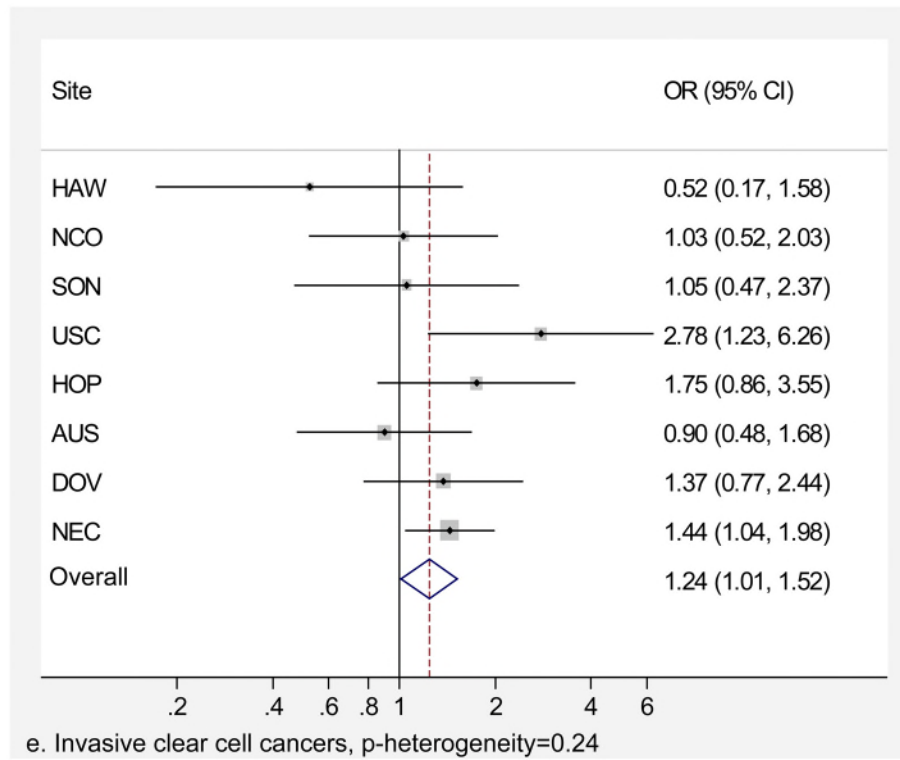
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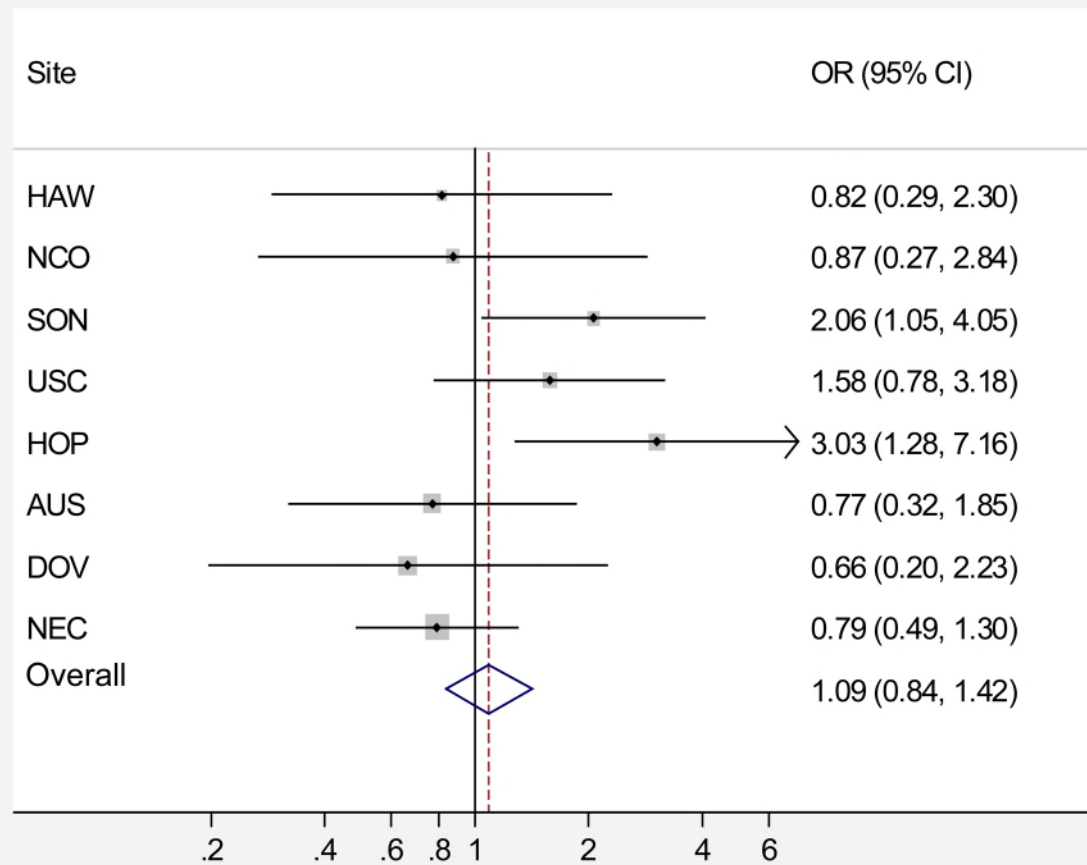
**Figure 1.**

Association between genital powder use and ovarian cancer risk in eight studies, p -heterogeneity=0.61. Adjusted for age (continuous), oral contraceptive duration (never use, <2yrs, 2–<5yrs, 5–<10yrs, ≥10yrs), parity (0, 1, 2, 3, 4+ children), tubal ligation history, BMI (quartiles), race/ethnicity (non-Hispanic white, Hispanic white, black, Asian, other). Studies listed in decreasing order of effect size standard error (funnel plot). No evidence of heterogeneity based on Conchran's Q statistic ($p=0.61$). AUS=Australian Cancer Study, DOV=Diseases of the Ovary and their Evaluation Study, HAW=Hawaii Ovarian Cancer Study, HOP=Hormones and Ovarian Cancer Prediction Study, NCO=North Carolina Ovarian Cancer Study, NEC=New England Case-Control Study of Ovarian Cancer, SON=Southern Ontario Ovarian Cancer Study









f. Invasive mucinous cancers, p-heterogeneity = 0.08

Figure 2.

Association between genital powder use and subgroups of ovarian cancer defined by behavior and histology. Estimates are adjusted for the same covariates as in the model presented in figure 1.

Table 1
Characteristics of eight studies included in the analysis of genital powder use and ovarian cancer

Study*	Diagnosis Years	Controls	Cases	Histology [†]		Behavior [‡]		Borderline	Question used to define genital powder use
				Serous	Mucinous	Endometrioid	Clear cell	Invasive	
AUS ^{††}	2002–2006	1449	1432	889 (62%)	174 (12%)	132 (9%)	78 (5%)	1158 (81%)	274 (19%) Have you ever used any sort of powder or talc on your genital area, in your underwear or on a sanitary pad or diaphragm?
DOV ^{††}	2002–2009	1841	1565	905 (58%)	186 (12%)	201 (13%)	87 (6%)	1153 (74%)	412 (26%) Before (reference date) did you ever use any of the following products routinely during one month or more? Powder on sanitary napkins or pads? Vaginal deodorant spray? Before (reference date) did you usually apply any powder to your genital (perineal) area after bathing? We are only interested in times when you did this for at least one year or longer. [§]
HAW	1993–2008	755	481	222 (46%)	87 (18%)	69 (14%)	47 (10%)	392 (82%)	89 (19%) Prior to (month/year of diagnosis) did you ever use talc, baby, or deodorizing powder dusted or sprayed on your body? By regularly I mean at least once a month for 6 months or more. Did you ever use talc, baby or deodorizing powder as a dusting powder to the genital or rectal area? As a dusting powder to sanitary napkins? As a dusting powder to underwear? On a diaphragm or cervical cap?
HOP	2003–2008	1489	735	433 (59%)	53 (7%)	75 (10%)	47 (6%)	568 (88%)	80 (12%) As an adult and prior to (reference month/year) did you ever use talc or baby powder or deodorizing powder with talc at least once a month for 6 months or more in any of the following ways: As a dusting powder or deodorizing spray more in any of the following ways: As a dusting powder or deodorizing spray to your genital or rectal areas? On your sanitary napkin? On your underwear? On your diaphragm or cervical cap?
NCO ^{††}	1999–2008	650	786	489 (62%)	71 (9%)	100 (13%)	65 (8%)	636 (81%)	148 (19%) Did you ever regularly use cornstarch, talc, baby or deodorizing powders (dusted or sprayed) at least 1 time per month for at least 6 months? If yes, please tell me if you used cornstarch, talc, baby or deodorizing powders in any of the following ways: directly to your genital or rectal areas? Applied to your sanitary napkins or tampons? Applied to birth control devices such as cervical cap or diaphragm? applied to your underwear?
NEC ^{††}	1992–2008	2329	2305	1234 (54%)	281 (12%)	352 (15%)	276 (12%)	1659 (77%)	486 (23%) Did you ever regularly use powder on your body or your underwear (at least once per month for any amount of time)? If yes, did you apply powder directly to your genital or rectal areas? To your sanitary napkins or tampons? To your underwear?
SON ^{††}	1989–1992	564	449	254 (57%)	80 (18%)	71 (16%)	29 (6%)	365 (81%)	84 (19%) Have you ever used sanitary napkins/tampons? If yes, could you tell me over what ages you've used them, for how many years, what percent of periods you've used them for, the usual number you've used for each period,

Study*	Diagnosis Years	Controls	Cases	Histology [†]		Clear cell	Behavior [‡]		Question used to define genital powder use
				Serous	Mucinous		Endometrioid	Invasive	
USC	1993–1997	782	772	396 (52%)	131 (17%)	75 (10%)	32 (4%)	549 (73%)	205 (27%)
whether they were deodorant pads/tampons, and if you used talcum powder or starch on them? Have you ever regularly used talcum powder or starch on your vaginal area after showering or bathing?									
Prior to (reference month/year), did you ever regularly use talc, baby, or deodorizing powder dusted or sprayed on your body? By regularly I mean at least once a month for 6 months or more. Did you ever use talc, baby, or deodorizing powder as a dusting powder to the genital or rectal area? as a dusting powder to sanitary napkins? as a dusting powder to underwear? on a diaphragm or cervical cap?									

* AUS = Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer), DOV = Diseases of the Ovary and their Evaluation, HAW = Hawaiian Ovarian Cancer Study, HOP = Hormones and Ovarian Cancer Prediction, NCO = North Carolina Ovarian Cancer Study, NEC = New England Case-Control Study of Ovarian Cancer, SON = Southern Ontario Ovarian Cancer Study, USC = University of Southern California Study of Lifestyle and Women's Health

[†] Cases listed by histology do not sum because mixed, other, undifferentiated, and unknown are not included.

[‡] Cases listed by behavior do not sum to the total number of cases because 267 cases are missing behavior information.

[§] In a separate series of questions, participants were asked about powder use with diaphragm storage. Duration was calculated from ages of use. Information on duration, frequency, and timing of use was only collected on genital/perineal powder use after bathing.

// Controls were asked "Have you ever regularly used..."

** NEC question varied slightly between the three study phases. Between 1992–1997 participants were asked, "As an adult and prior to (reference month/year), did you regularly use talc, baby, or deodorizing powders dusted or sprayed to your body in any of the following ways:." Between 1998–2003, women were asked "Did you regularly apply cornstarch, talc, baby, or deodorizing body powder at least one time per month for six months or longer? If yes, please tell me if you regularly applied cornstarch, talc, baby or deodorizing body powders in any of the following ways:." Between 2003–2008 participants were asked the question listed above.

^{††} These studies previously published on genital powder use and ovarian cancer risk. AUS, DOV, and NEC provided new data to the pooled analyses presented here that were not included in previous publications.

Table 2

Characteristics of cases and controls included in the pooled analysis *

	Controls (N=9,859)	Cases (N=8,525)
	Mean (std) or N (%)	Mean (std) or N (%)
Age	55 (12)	55 (12)
OC use		
Never	2995 (30)	3411 (40)
Ever	6864 (70)	5114 (60)
Parous		
No	1468 (15)	2196 (26)
Yes	8391 (85)	6329 (74)
Tubal Ligation		
No	7359 (75)	6994 (82)
Yes	2500 (25)	1531 (18)
Body Mass Index	26.5 (6.1)	27.0 (6.6)
Race/Ethnicity		
Non-Hispanic White	8629 (88)	7433 (87)
Hispanic White	197 (2)	214 (3)
Black	273 (3)	268 (3)
Asian	350 (4)	313 (4)
Other †	407 (4)	291 (4)
Powder use ‡		
Never use	5815 (59)	4643 (54)
Non-genital use only	1533 (16)	1282 (15)
Genital use	2511 (25)	2600 (31)

* All characteristics listed except age differed significantly (<0.01) between cases and controls. Cases include both borderline and invasive ovarian cancers.

† There are six cases and three controls missing race/ethnicity information.

‡ Categories for non-genital and genital powder use are mutually exclusive.

Table 3

Association between powder use and risk of ovarian cancer (borderline and invasive combined) by study site

Site	Controls (%) (N= 9,859)	Cases (%) (N= 8,525)	Age-adjusted OR (95% CI)*	Multivariate OR (95% CI)*
AUS				
No powder use	305 (21)	300 (21)	1.00	1.00
Non-genital use only	486 (34)	427 (30)	0.85 (0.69–1.05)	0.92 (0.74–1.14)
Genital use	658 (45)	705 (49)	1.04 (0.85–1.26)	1.13 (0.92–1.38)
DOV [†]				
No powder use	1544 (83)	1293 (83)	1.00	1.00
Genital use	297 (16)	272 (17)	1.14 (0.95–1.37)	1.13 (0.93–1.36)
HAW				
No powder use	489 (65)	326 (68)	1.00	1.00
Non-genital use only	154 (20)	81 (17)	0.79 (0.58–1.07)	0.69 (0.50–0.96)
Genital use	112 (15)	74 (15)	0.99 (0.72–1.37)	0.99 (0.70–1.41)
HOP				
No powder use	989 (66)	439 (60)	1.00	1.00
Non-genital use only	184 (13)	102 (14)	1.23 (0.94–1.61)	1.23 (0.93–1.62)
Genital use	316 (21)	194 (26)	1.37 (1.11–1.69)	1.34 (1.07–1.67)
NCO				
No powder use	391 (60)	469 (60)	1.00	1.00
Non-genital use only	137 (21)	122 (16)	0.75 (0.57–0.99)	0.74 (0.56–0.99)
Genital use	122 (19)	195 (25)	1.33 (1.03–1.74)	1.37 (1.05–1.80)
NEC				
No powder use	1239 (53)	1129 (49)	1.00	1.00
Non-genital use only	454 (19)	421 (18)	1.02 (0.87–1.19)	1.04 (0.88–1.22)
Genital use	636 (27)	755 (33)	1.30 (1.14–1.49)	1.28 (1.12–1.47)
SON [†]				
No powder use	364 (65)	252 (56)	1.00	1.00
Genital use	200 (35)	197 (44)	1.43 (1.11–1.85)	1.35 (1.03–1.76)
USC				
No powder use	494 (63)	435 (56)	1.00	1.00
Non-genital use only	118 (15)	129 (17)	1.25 (0.94–1.66)	1.14 (0.85–1.52)
Genital use	170 (22)	208 (27)	1.39 (1.10–1.77)	1.36 (1.06–1.74)
Pooled [‡]				
No powder use	5815 (59)	4643 (54)	1.00	1.00
Non-genital use only	1533 (16)	1282 (15)	0.98 (0.90–1.07)	0.98 (0.89–1.07)
Genital use	2511 (25)	2600 (31)	1.25 (1.16–1.34)	1.24 (1.15–1.33)

* Study-specific estimates were determined using unconditional logistic regression and pooled ORs were estimated using conditional logistic regression conditioned on 5yr age groups and study. Multivariate models are adjusted for age (continuous), oral contraceptive duration (never use, <2yrs, 2–<5yrs, 5–<10yrs, ≥10yrs), parity (0,1,2,3,4+ children), tubal ligation history (no, yes), BMI (quartiles), race/ethnicity (non-Hispanic white, Hispanic white, black, Asian, other).

[†] Information on non-genital powder use was not collected in the SON and DOV study

[‡] p-value for heterogeneity between multivariate study specific ORs equal to 0.61; calculated using Conchran's Q statistic test

Table 4
Association between powder use and risk of ovarian cancer by behavior and histology

	Model 1*			Model 2*		
	No powder use n (%)	Genital powder use n (%)	OR (95% CI) [†]	No genital powder use n (%)	Genital powder use n (%)	OR (95% CI) [†]
Controls	5815 (59)	2511 (25)		7348 (75)	2511 (25)	
All borderline cases	1035 (58)	504 (28)	1.29 (1.14–1.48)	1247 (72)	504 (28)	1.30 (1.15–1.47)
Serous	567 (57)	300 (30)	1.46 (1.24–1.72)	700 (70)	300 (30)	1.45 (1.24–1.69)
Mucinous	409 (60)	184 (27)	1.17 (0.96–1.42)	502 (73)	184 (27)	1.19 (0.98–1.43)
All invasive cases	3470 (54)	2009 (31)	1.21 (1.12–1.32)	4471 (69)	2009 (31)	1.23 (1.14–1.32)
Serous	1952 (53)	1197 (32)	1.20 (1.09–1.32)	2519 (68)	1197 (32)	1.24 (1.13–1.35)
Mucinous	206 (57)	94 (26)	1.09 (0.84–1.42)	269 (74)	94 (26)	1.06 (0.82–1.36)
Endometrioid	568 (55)	304 (30)	1.22 (1.04–1.43)	723 (70)	304 (30)	1.20 (1.03–1.40)
Clear Cell	327 (54)	187 (31)	1.24 (1.01–1.52)	420 (69)	187 (31)	1.26 (1.04–1.52)

* In model 1, the reference group is restricted to women with no powder use except for the DOV and SON studies as these did not collect data on non-genital powder use. The number of cases who reported non-genital powder use was 212 (13%) of all borderline cases, 133 (13%) serous borderline, 93 (14%) mucinous borderline, 1001 (15%) of all invasive, 567 (15%) serous invasive, 63 (17%) mucinous invasive, 155 (15%) endometrioid invasive, 93 (15%) clear cell invasive. In model 2, the reference group includes all women who did not use genital powders (non-users and non-genital users combined).

[†] ORs were estimated using conditional logistic regression conditioned on 5yr age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2yrs, 2–<5yrs, 5–<10yrs, ≥10yrs), parity (0,1,2,3,4+ children), tubal ligation history (no, yes), BMI (quartiles), race/ethnicity (non-Hispanic white, Hispanic white, black, Asian, other).

Table 5

Association between estimated lifetime applications of genital powder and risk of ovarian cancer (borderline and invasive combined)

Lifetime number of applications*	All Cases (N= 7,587)		Non-mucinous cases (N= 6,361)	
	Controls (%)	Cases (%)	OR [†] (95 % CI)	OR [†] (95 % CI)
Never users	6175 (76)	5384 (71)	1.00	1.00
Quartile 1	509 (6)	534 (7)	1.14 (1.00–1.31)	1.18 (1.02–1.36)
Quartile 2	512 (6)	541 (7)	1.23 (1.08–1.41)	1.22 (1.06–1.41)
Quartile 3	497 (6)	542 (7)	1.22 (1.07–1.40)	1.22 (1.06–1.40)
Quartile 4	486 (6)	586 (8)	1.32 (1.16–1.52)	1.37 (1.19–1.58)
p-trend [‡]			0.17	0.17

* Age specific 25th, 50th and 75th percentile cutpoints are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41–50 years; 720, 3,600, and 10,800 for 51–60 years; 1,440, 5,760, and 14,440 for 61–70; 840, 7,200, and 18,000 for > 70 years.

[†] ORs were estimated using conditional logistic regression conditioned on 5yr age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2yrs, 2–<5yrs, 5–<10yrs, ≥10yrs), parity (0,1,2,3,4+ children), tubal ligation history (no, yes), BMI (quartiles), race/ethnicity (non-Hispanic white, Hispanic white, black, Asian, other).

[‡] Trend excludes never users.

Exhibit 45

REPORTS

Prospective Study of Talc Use and Ovarian Cancer

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Background: Perineal talc use has been associated with an increased risk of ovarian cancer in a number of case-control studies; however, this association remains controversial because of limited supporting biologic evidence and the potential for recall bias or selection bias in case-control studies. In this study, we conducted a prospective analysis of perineal talc use and the risk of ovarian cancer. **Methods:** The Nurses' Health Study is a prospective study of 121 700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. Talc use was ascertained in 1982 by use of a self-administered questionnaire: after exclusions, 78 630 women formed the cohort for analysis. Three hundred seven epithelial ovarian cancers subsequently diagnosed in this cohort through June 1, 1996, were confirmed by medical record review and met inclusion criteria. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs). **Results:** In 1982, 40.4% ($n = 31\,789$) of the cohort reported ever using talc, and 14.5% ($n = 11\,411$) reported ever using talc daily. We observed no overall association with ever talc use and epithelial ovarian cancer (multivariate RR = 1.09; 95% CI = 0.86–1.37) and no increase in risk of ovarian cancer with increasing frequency of use. There was a modest elevation in risk for ever talc use and invasive serous ovarian cancer (multivariate RR = 1.40; 95% CI = 1.02–1.91). The risk of epithelial ovarian cancer for talc users was not greater among women who had never had a tubal ligation (multivariate RR = 0.97; 95% CI = 0.71–1.32). **Conclusion:** Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk

overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer. [J Natl Cancer Inst 2000;92:249–52]

Talc was originally implicated as a possible ovarian carcinogen because of its chemical similarity to asbestos, which has been linked to ovarian cancer in occupational settings and is associated with mesotheliomas histologically resembling epithelial ovarian cancers (1–3). Perineal use of talcum powder has been positively associated with ovarian cancer risk in a number of case-control studies (4–13), although the magnitude of the associations has been modest, with odds ratios ranging from 1.2 to 1.9, and not all results reached statistical significance (5,6,8). Despite this relative consistency among studies, the limited supporting biologic evidence, together with the possibility of recall and selection bias in case-control studies (1), has raised questions about the plausibility of the association. We, therefore, prospectively examined the relationship between perineal talc use and ovarian cancer risk in a large cohort of U.S. women.

METHODS

The Nurses' Health Study, established in 1976, is a prospective cohort of 121 700 registered nurses living in 11 of the larger states in the United States. Questionnaires were mailed to married, female nurses aged 30–55 years, requesting information on health-related issues, including medical history and potential risk factors for cancer. Follow-up questionnaires have been mailed every 2 years to update information on exposures and to ascertain newly diagnosed diseases. The study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, MA.

Ascertainment of cases. We sought medical records from all women who reported a diagnosis of ovarian cancer or who were deceased in each follow-up cycle. Records were reviewed by physicians unaware of exposure status. Histologic subtypes were determined from pathology reports, and epithelial ovarian cancers were classified as serous cancers (including cystadenocarcinoma and papillary adenocarcinoma), mucinous cancers (including adenocarcinoma and mucinous papillary adenocarcinoma), and endometrioid cancers (clear cell and other types, including mixed epithelial tumors). Borderline histologic tumors are included in the analysis. Deaths are reported by relatives and postal authorities, as well as a search of the National Death Index. Mortality follow-up is estimated to be 98% complete in this cohort (14). Cases of epithelial ovarian cancer (International Classification of Diseases Code, ICD183.0), confirmed by medical rec-

ord review or death certificate, occurring between the return of the 1982 questionnaire and June 1, 1996, were included in the analysis.

Exclusions. Women who did not respond to the question on talc use in 1982 were excluded from this analysis. We also excluded women who had reported a diagnosis of cancer (other than nonmelanoma skin cancer) before 1982, as well as women who reported bilateral oophorectomy, surgery with an unknown number of ovaries removed, and a history of radiation therapy. Validity of self-reported surgical menopause has been assessed previously, and agreement with medical records was more than 97% (15). These exclusions were updated every 2 years. At baseline, 78 630 women were eligible for the analysis. The resulting population after exclusions contributed 984 212 person-years of follow-up and 307 cases of epithelial ovarian cancer.

Ascertainment of talc exposure. Use of talcum powder was ascertained on the 1982 questionnaire in the following ways: "Have you ever commonly used talcum, baby powder, or deodorizing powder *a*) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or *b*) to apply on sanitary napkins? No, Yes." We classified "ever talc use" as ever talc use on either the perineal area or sanitary napkins.

Other covariates. Potential risk factors and confounders of the association between ovarian cancer and exposures of interest in this analysis also were obtained from the biennial questionnaires and were updated every 2 years where relevant. Oral contraceptive use was asked every 2 years from 1976 through 1982, by which time use was rare. Tubal ligation history was asked as part of a question on methods of contraception from 1976 through 1984, and, in 1994, women were asked if they had ever

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had a tubal ligation and, if so, at what age. Family history of ovarian cancer was not asked until 1992. Parity was defined as the number of pregnancies lasting 6 months or more and was asked through 1984.

Statistical analysis. Incidence rates (number of cases for each category of exposure divided by person months of follow-up in that cycle) were calculated for each category, adjusting for age in 5-year intervals. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs) of disease for each exposure category (16). For age-adjusted analyses, we categorized variables as follows: parity (0, 1–2, or ≥ 3), oral contraceptive use (never, past, or current), tubal ligation (yes or no), postmenopausal hormone use (never, past, or current), cigarette smoking (never, past, or current), and body mass index, i.e., weight in kilograms/height in meters squared (<21 , 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥ 29 kg/m²). In multivariate analyses, we adjusted for age (years) and for potential risk factors by use of indicator variables for each category as described above, except for parity (0, 1–2, 3–4, or ≥ 5) and duration of oral contraceptive use (never or <3 , 3–5, or >5 years), for which we used a larger number of categories to more appropriately control for confounding. In addition we controlled for age at menarche, duration of breast-feeding, and age at menopause. However, since this did not alter the estimates for talc use, further models did not control for these variables. Body mass index and duration of oral contraceptive use were also entered as continuous variables, and similar estimates were obtained. All RRs reported are multivariate unless otherwise stated. *P* values reported are two-sided.

RESULTS

Three hundred seven women developed ovarian cancer in the cohort from 1982 through 1996 who responded to the 1982 questionnaire on talc use. In 1982, 40.4% ($n = 31\,789$) of the baseline cohort reported ever using talc, of which 14.5% ($n = 11\,411$) were ever daily talc users. Talc use was associated with higher body mass index and inversely associated with current cigarette smoking (Table 1).

We did not observe an overall association with ever use of talc and epithelial ovarian cancer (RR = 1.09; 95% CI = 0.86–1.37). There was also no elevation in risk among daily users of perineal talc, and no trend was seen with increasing frequency of use (Table 2). Talc use on sanitary napkins was inversely related to ovarian cancer, but the association was statistically nonsignificant. Exclusion of use of talc on sanitary napkins from the ever use of talc variable did not substantially alter the results. We also evaluated the risk for women who used both perineal talc and talc on sanitary napkins but did not see an effect compared with never users of talc (RR = 0.90; 95% CI = 0.59–1.37).

When we stratified by histologic sub-

Table 1. Age-standardized prevalence of ovarian cancer risk factors according to perineal talc use in 1982*

	Ever perineal talc use, % [†] ($n = 31\,789$)	No perineal talc use, % ($n = 46\,841$)
Parity		
0	6.3	6.4
1–2	35.0	35.2
≥ 3	58.7	58.4
Oral contraceptive use		
Current	0.5	0.6
Past	49.2	49.8
Never	50.4	49.6
Hormone use, postmenopausal women only		
Current	12.1	12.9
Past	20.5	20.4
Never	67.4	66.7
Tubal ligation, yes	17.6	17.6
Cigarette smoking		
Never	44.9	43.2
Past	30.3	28.3
Current	24.9	28.5
Body mass index quintiles, kg/m ²		
<21.0	16.0	22.1
21.0–22.9	20.9	25.4
23.0–24.9	20.1	20.6
25.0–28.9	22.8	19.6
≥ 29	19.8	12.0

*Numbers do not always add up to 100% because of missing data or rounding.

[†]Ever talc use coded as either talc use on perineal area or talc use on sanitary napkins.

Table 2. Talc use and ovarian cancer: 1982 through 1996 (all subtypes included)*

	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR [†] (95% CI)
Talc use on perineum				
Never	186	608 020	1.0 (referent)	1.0 (referent)
<1 /wk	43	128 923	1.10 (0.79–1.53)	1.14 (0.81–1.59)
1–6/wk	30	105 186	0.95 (0.65–1.40)	0.99 (0.67–1.46)
Daily	48	142 083	1.09 (0.79–1.49)	1.12 (0.82–1.55)
Talc use on sanitary napkins				
No	242	781 421	1.0 (referent)	1.0 (referent)
Yes	32	111 399	0.89 (0.62–1.29)	0.89 (0.61–1.28)
Ever perineal talc use				
No	179	586 758	1.0 (referent)	1.0 (referent)
Yes	128	397 454	1.05 (0.84–1.32)	1.09 (0.86–1.37)
Talc use, perineal and sanitary napkins				
None	179	586 758	1.0 (referent)	1.0 (referent)
Either talc use on perineum or use on sanitary napkins	103	307 317	1.11 (0.87–1.41)	1.15 (0.90–1.46)
Use on both sanitary napkins and perineum	25	90 137	0.89 (0.58–1.35)	0.90 (0.59–1.37)

*RR = relative risk; CI = confidence interval.

[†]Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ≥ 5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21 , 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥ 29 kg/m²), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

type, we observed a modest increase in risk for ever talc use for serous invasive cancers (RR = 1.40; 95% CI = 1.02–1.91) but not for all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers (Table 3). For women who reported ever daily use

of talc, the RR of invasive serous cancer was 1.49 (95% CI = 0.98–2.26). The RRs for ever talc users of less than once per week and one to six times per week were 1.29 (95% CI = 0.81–2.04) and 1.49 (95% CI = 0.77–2.11), respectively (*P* for trend = .05).

Table 3. Talc use and ovarian cancer: 1982–1996 (by histologic subtype)*

Histologic subtype	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
All serous cancers, ever perineal talc use				
No	101	586 771	1.0 (referent)	1.0 (referent)
Yes	84	397 459	1.23 (0.92–1.64)	1.26 (0.94–1.69)‡
Serous invasive cancers, ever perineal talc use				
No	84	586 771	1.0 (referent)	1.0 (referent)
Yes	76	397 459	1.33 (0.98–1.82)	1.40 (1.02–1.91)‡
Endometrioid cancers, ever perineal talc use				
No	26	586 771	1.0 (referent)	1.0 (referent)
Yes	16	397 459	0.91 (0.49–1.69)	0.91 (0.49–1.87)
Mucinous cancers, ever perineal talc use				
No	30	586 771	1.0 (referent)	1.0 (referent)
Yes	20	397 459	0.98 (0.56–1.73)	0.93 (0.53–1.66)

*RR = relative risk; CI = confidence interval.

†Multivariate analyses controlling for age (years), parity (0, 1–2, or ≥ 3), oral contraceptive use (never or ever), and tubal ligation history (yes or no).

‡Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ≥ 5), duration of oral contraceptive use (never or < 3 y, 3–5 y, or > 5 y), body mass index (body weight in kilograms/height in meters squared: < 21 , 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥ 29 kg/m²), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Because the talc hypothesis depends on the ability of fibers to migrate up a patent genital tract to the ovaries, we evaluated the risk among women who had reported a tubal ligation and those who had not. Women who were ever talc users and had never had a tubal ligation were not at increased risk of epithelial ovarian cancer compared with women who had not used talc (RR = 0.97; 95% CI = 0.71–1.32). There was no evidence of heterogeneity of RRs between women who had a tubal ligation and women who did not. In addition, when women who had had a tubal ligation or simple hysterectomy were excluded from the analysis, the RR for ever talc use was 1.15 (95% CI = 0.89–1.49). For serous invasive cancers, the RR for women who had never had a tubal ligation was similar to that for women without a tubal ligation; however, the number of case patients who had had a tubal ligation was small (data not shown).

Cosmetic talc may have been more likely to contain asbestos fibers prior to 1976, before voluntary guidelines were proposed (9). As a proxy for early talc use, we assessed risk among women 45 years old or older in 1982. There was no evidence that older women in 1982 were at greater risk of ovarian cancer overall; the RR for ever talc use compared with never talc use for women under 45 years was 0.95 (95% CI = 0.59–1.53) and among women 45 years old or older was 1.13 (95% CI = 0.86–1.47). However, women 45 years old or older in 1982 who

ever used talc had a higher risk of serous invasive cancer (RR = 1.51; 95% CI = 1.07–2.15). There was no evidence of effect modification by oral contraceptive use, body mass index, or cigarette smoking for epithelial cancers overall.

DISCUSSION

To our knowledge, this is the first prospective analysis of talc use and ovarian cancer, and it addresses some of the potential limitations of previous case-control studies. Because we ascertained talc exposure prior to case diagnosis, the possibility for recall bias, which has been raised as a potential explanation for previous positive findings in case-control studies (1), is eliminated, and selection bias is reduced. We controlled for known or suspected ovarian cancer risk factors in the analysis, such as parity, oral contraceptive use, tubal ligation history, and body mass index, reducing the potential for uncontrolled confounding.

However, there are several important limitations to our study. The questions on talcum powder use referred to ever use, and we cannot determine the age at which women began using talc or the duration of use. Thus, we were unable to assess the potential effect of talc use before first pregnancy, which has been shown to be a stronger risk factor for ovarian cancer than use after pregnancy in one study (13). The number of lifetime applications of talc has also been associated with increased risk of ovarian cancer in some

previous studies (9,13). Our relatively short follow-up period may be inadequate to detect an association if the latency for development of ovarian cancer is more than 15 years. Although we controlled for tubal ligation history, the tubal ligation question was asked as part of a question on contraceptive use; therefore, postmenopausal women and some premenopausal women who were not sexually active may not have responded to the question. Substantial residual confounding is unlikely, since there was no overall association between talc use and tubal ligation in this study. In addition, we excluded women who were postmenopausal in 1976 from analyses stratified by tubal ligation history. Finally, the prevalence of talc use in our study is somewhat higher than that in other studies and may reflect the fact that we asked about frequency of ever use rather than current regular use; this may have contributed to an attenuation of risk due to misclassification of exposure.

The potential effect of talc on the ovaries depends on migration of talc fibers through a patent genital tract, and we would, therefore, expect a stronger association among women without a tubal ligation who had used talc. However, no effect modification was seen by history of tubal ligation. Because we did not have the date of tubal ligation, some women may have begun talc use only after tubal ligation, potentially resulting in misclassification of talc use and attenuation of the RRs.

Since the first study showing an almost twofold increase in risk of ovarian cancer with any perineal talc use (4), most case-control studies have demonstrated positive associations with talc use (4–13), although not all have been statistically significant (5,6,8). Several studies (9,17–20) found no overall association between any genital talc use and ovarian cancer. We did not observe a dose-response relationship with talc use, and previous studies also have been inconsistent in this regard. Some studies (9,13,17) have demonstrated statistically insignificant trends in risk with increased frequency of talc use, duration of use, and measures of “total lifetime applications,” while other studies (6,8) have not observed a statistically significant dose response.

With regard to histologic subtypes, a recent study by Cramer et al. (13) observed the greatest risk for talc use and invasive serous cancer; however, other

studies found increased risks for endometrial cancers (9,12), serous cancers (7), and invasive cancers of all subtypes (12). Since serous cancers, which account for more than half of all invasive ovarian cancers, most resemble mesotheliomas, it could be hypothesized that this subtype may be most likely associated with talc use. In our stratification by subtype, we did observe a modest positive association with serous invasive cancers and ever talc use as well as a borderline significant trend for increasing frequency of ever use.

The biologic evidence for the association of talc and ovarian cancer is incomplete. Asbestos has been linked to ovarian cancer in occupational settings and is associated with peritoneal tumors similar to ovarian cancer (2,3,21). Because of the chemical similarity of talc and asbestos, talc also has been implicated as a possible ovarian carcinogen. Talc is able to migrate through the genital tract and gain access to the ovaries because talc fibers have been detected in benign and malignant ovarian tissue (22), although no relation between reported levels of talc exposure and ovarian talc counts has been observed (23). There have been few studies (24,25) of talc exposure in animals, and these studies have not demonstrated an increase in ovarian cancer among animals subjected to chronic talc exposure. These data should be interpreted cautiously because there are important anatomic and physiologic differences between rodents and humans, and talc in animals is often administered at high dose via aerosol exposure (24).

In summary, we did not observe an overall association between epithelial ovarian cancer and ever use of talc, and there was no apparent dose response, although we lacked information on duration of talc use. In analyses stratified by histologic subtype, we observed a modest positive association between invasive serous cancer and ever talc use. Our results provide little support for any substantial association between perineal talc use and

ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancers.

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NOTES

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Exhibit 46



Original Contribution

Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype

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Previous epidemiologic studies suggest that the major histologic subtypes of epithelial ovarian cancer may have different risk factor profiles; however, no known prospective study has systematically examined differences in risk by subtype. The authors used Cox proportional hazards regression, stratified by histologic subtype and time period, to examine the association between ovarian cancer risk factors and incidence of serous invasive, endometrioid, and mucinous ovarian cancers in the US Nurses' Health Study (1976–2006) and Nurses' Health Study II (1989–2005). For each exposure, they calculated *P*-heterogeneity using a likelihood ratio test comparing models with separate estimates for the 3 subtypes versus a single estimate across subtypes. Analysis included 221,866 women and 721 cases with the histologies of interest (496 serous invasive, 139 endometrioid, 86 mucinous). In analyses of reproductive/hormonal exposures, the associations with age, duration of breastfeeding, age at natural menopause, and duration of estrogen use differed significantly by subtype (all *P*-heterogeneity = 0.05). The associations with several nonreproductive exposures also appeared to vary by subtype, but only the association with smoking differed significantly (*P*-heterogeneity = 0.03). Results suggest that associations with several ovarian cancer risk factors vary by subtype, and these differences are consistent with known similarities between each major histologic subtype and its normal tissue counterpart.

adenocarcinoma, mucinous; carcinoma, endometrioid; cystadenocarcinoma, serous; histology; ovarian neoplasms

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

Epithelial ovarian cancers often are analyzed as a single outcome in epidemiologic studies, despite evidence of differences in their natural history, morphology, and gene/protein expression (1–4). The most common histologic subtypes of epithelial ovarian cancer each resemble a different normal tissue in morphology and gene expression (4, 5), and previous studies suggest their etiology may differ as well. In a pooled analysis of 10 case-control studies, oral contraceptive use and parity were inversely associated with all subtypes, whereas associations with nonreproductive exposures, particularly body mass index and smoking, differed by subtype (6). Other studies have reported differences in associations with both reproductive and nonreproductive exposures for mucinous versus nonmucinous cancers (7–12).

Although these studies suggest that some associations differ by subtype, the data are inconsistent (6–10, 13, 14), and no known comprehensive, prospective analysis of differences in risk factors by histologic subtype has been pub-

lished. In addition, most prior studies analyzed each subtype separately and did not report a statistical test comparing results across subtypes. We therefore used polytomous regression models to examine the association between known and suspected risk factors for ovarian cancer and incidence of the serous invasive, endometrioid, and mucinous subtypes in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

MATERIALS AND METHODS

Study population

The NHS was established in 1976 and the NHSII in 1989 among 121,700 US female registered nurses aged 30–55 years and 116,430 US female registered nurses aged 25–42 years, respectively. Participants completed an initial questionnaire and biennial follow-up questionnaires,

providing information on lifestyle factors and disease diagnoses. Follow-up is high in both cohorts; we obtained 95.2% of the total possible person-years through June 2006 in the NHS and 93.6% through June 2005 in the NHSII. The Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital, Boston, Massachusetts, approved both studies.

Exposure data

We obtained information on exposures of interest from the biennial questionnaires. At baseline, participants reported their birth date, age at menarche, and height. We requested information on parity, oral contraceptive use, tubal ligation, hysterectomy/oophorectomy, menopausal status, age at menopause, postmenopausal hormone use, weight, physical activity, smoking status, and family history of breast/ovarian cancer on multiple questionnaires during follow-up. In our analysis, we updated values for these covariates when new data were available and otherwise carried forward values from the previous cycle. We requested data on total duration of breastfeeding across all pregnancies in 1986 (NHS) and 1993 (NHSII) and on duration of breastfeeding for each child in 1997 (NHSII only). Information on frequency of genital talc use was collected in 1982 (NHS only).

Identification of ovarian cancer cases

We collected information on new ovarian cancer diagnoses on each questionnaire. For all reported cases, as well as deaths due to ovarian cancer identified through family members, the National Death Index (15, 16), or the US Postal Service, we obtained medical records related to the diagnosis. A gynecologic pathologist (J. H.) blinded to exposure status reviewed the medical records to confirm the diagnosis, stage, histologic type/subtype, and invasiveness (17). Our analysis included cases of epithelial ovarian cancer ($n = 885$) and primary peritoneal cancer ($n = 39$) confirmed by pathology report review and diagnosed between baseline and June 2006 (NHS) or 2005 (NHSII).

Statistical analysis

Participants accrued person-time from the return date of the baseline questionnaire until the date of ovarian cancer diagnosis, diagnosis of any other cancer (excluding non-melanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up. At baseline, we excluded women with bilateral oophorectomy (NHS: $n = 7,669$; NHSII: $n = 2,229$), menopause due to pelvic irradiation (NHS: $n = 99$; NHSII: $n = 30$), or cancer other than nonmelanoma skin cancer (NHS: $n = 3,314$; NHSII: $n = 1,050$). In addition, we excluded women with missing data on any exposure of interest except breastfeeding duration, talc use, and family history of ovarian cancer, which were not collected at baseline, and age at natural menopause, which was missing for women with a hysterectomy before menopause. We included missing indicators for these 4 exposures in our models to avoid excluding too many

women from the analysis. Participants contributed person-time only for follow-up periods for which data were complete. Furthermore, we excluded person-time ($< 0.3\%$ of the total) when any continuous variable had an outlying value, using the generalized extreme studentized deviate many-outlier detection approach (18).

In analyses of reproductive/hormonal exposures, we modeled age, parity among parous women, duration of breastfeeding, duration of oral contraceptive use, age at natural menopause, and duration of postmenopausal use of unopposed estrogens as continuous variables to minimize the number of parameters in the model. We used binary variables to model menopausal status (postmenopause vs. premenopause/perimenopause), cohort (NHS vs. NHSII), and parity, tubal ligation, and hysterectomy without bilateral oophorectomy (yes/no). Because of evidence of a nonlinear association with age, we used a spline with a single knot at age 50 years to estimate linear associations with age separately for women younger than age 50 years versus 50 years of age or older.

In an alternative analysis, we modeled ovulatory years and duration of menopause instead of age, parity, duration of oral contraceptive use, and age at natural menopause. We calculated ovulatory years as current age (if premenopausal) or age at natural menopause minus age at menarche, years of oral contraceptive use, and parity (1 year per pregnancy), and we included a separate variable for total duration of breastfeeding. We calculated duration of menopause as current age minus age at natural menopause for postmenopausal women, and we coded premenopausal/perimenopausal women as 0. For women with an unknown age at natural menopause because of hysterectomy before menopause, we excluded person-time after hysterectomy.

For the nonreproductive exposures, we modeled body mass index (weight (kg)/height (m)²) and physical activity (cumulative average metabolic equivalent task-hours/week) continuously, regular genital talc use ($< \text{once/week}$ vs. $\geq \text{once/week}$) and family history of breast/ovarian cancer (yes/no) as binary variables, and smoking status as 2 indicator variables for past or current (vs. never) smoking. Metabolic equivalent task-hours captures both duration and intensity of activity (3 metabolic equivalent task-hours is equivalent to walking 2–2.9 mph for 1 hour (1 mile = 1.6 km)), and cumulative average levels better reflect long-term activity and minimize within-person variation. In the NHS, data on metabolic equivalent task-hours were not available until 1986; we therefore assigned all participants 0 activity from 1976 to 1986 and secondarily evaluated the association with physical activity with follow-up beginning in 1986.

We used Cox proportional hazards regression, stratified by time period, to model the incidence rate ratio and 95% confidence interval of epithelial ovarian cancer for each exposure in the NHS and NHSII combined. We then restricted the analysis to cases with serous invasive/poorly differentiated, endometrioid, or mucinous histology and used Cox proportional hazards regression, stratified by type of outcome and time period, to allow for different associations by histologic subtype (19). We used data augmentation, such that each participant had a separate observation for each subtype. We coded the event variable as 1 (failed) if

the participant was diagnosed with the histologic subtype corresponding to that data row and as 0 otherwise; cases were censored for other subtypes at the time of diagnosis.

We compared a model that assumed different associations for all exposures by histologic subtype (full model) with a model with a single estimate across subtypes for one exposure at a time (reduced model). We calculated the P -heterogeneity using a likelihood ratio test, with the degrees of freedom equal to the difference between the numbers of parameters in the 2 models. Using a stepwise-down approach, we set exposures with a nonsignificant P -heterogeneity to have a single estimate across subtypes, so that the final model estimated 3 separate associations for exposures that differed significantly by subtype and a single estimate for all other exposures. All P values were 2-sided and were considered statistically significant if < 0.05 .

We evaluated goodness of fit by calculating the area under the receiver operating characteristic curve (AUC) for all cancers and stratified by subtype. For each observation, we determined a risk score using parameter estimates from the model, and we used the risk scores to calculate the Wilcoxon rank sum test statistic W by 5-year age group t . We calculated the Mann-Whitney $U_t = W_t - \frac{m_t(m_t+1)}{2}$ and $\hat{\theta}_t = \frac{U_t}{m_t n_t}$, where $\hat{\theta}_t$ is the probability that a random case has a higher risk score than a random control within age group t . We calculated the variance of $\hat{\theta}_t$ under the alternative hypothesis (20), and we calculated the overall AUC as the weighted average of $\hat{\theta}_t$ across t with weights $= 1/\text{var}(\hat{\theta}_t)$.

We did not have adequate power to examine associations with clear-cell cancers separately because of the small number of cases ($n = 48$). However, we evaluated differences between serous versus nonserous (endometrioid/mucinous/clear-cell) and mucinous versus nonmucinous (serous/endometrioid/clear-cell) cancers. In secondary analyses, we examined differences between all 4 subtypes for the reproductive exposures only.

RESULTS

Our analysis included 221,866 women with 924 incident cases of confirmed epithelial ovarian cancer (NHS: 108,870 women and 797 cases; NHSII: 112,996 women and 127 cases). Of the cases of cancer, 496 were serous invasive (54%), 139 were endometrioid (15%), and 86 were mucinous (9%). The remaining 203 cases of cancer included 48 clear cell (5% of total), 71 noninvasive serous (8%), 21 carcinosarcoma (2%), 17 mixed (2%), and 46 other/unknown (5%).

In general, baseline characteristics of cases versus non-cases were similar to those expected based on previous studies of known risk factors (Table 1). NHSII participants were younger than NHS participants and were more likely to have used oral contraceptives or have had a tubal ligation, were less likely to be parous or to smoke, were more physically active, and had lower mean parity but a longer mean duration of breastfeeding among parous women.

When we compared baseline characteristics of women subsequently diagnosed with a serous invasive, endometrioid, or mucinous tumor (Table 1), we found that serous

invasive cases were slightly older, had higher parity, and were more physically active than endometrioid/mucinous cases. Endometrioid cases had a longer mean duration of estrogen use (NHS only) and a higher mean body mass index (NHSII only), were less likely to be parous (NHS only) or to have smoked, and were more likely to have a family history of breast cancer. Mucinous cases had a shorter mean duration of estrogen use (NHS only) and breastfeeding and were less physically active, less likely to have had a hysterectomy, and were more likely to have regularly used talc or to currently smoke (NHS only).

The associations with age (P -heterogeneity < 0.001), duration of breastfeeding (P -heterogeneity $= 0.03$), age at natural menopause (P -heterogeneity $= 0.05$), and duration of estrogen use (P -heterogeneity $= 0.009$) differed significantly by subtype, whereas other exposures (e.g., oral contraceptive use) exhibited similar associations across the 3 subtypes (Table 2). Age among women less than 50 years was more strongly associated with serous invasive (incidence rate ratio (RR) $= 1.15$ per year, 95% confidence interval (CI): 1.10, 1.19) and endometrioid (RR $= 1.12$ per year, 95% CI: 1.06, 1.17) tumors than mucinous tumors. Among women aged 50 years or older, age was associated with a modest increase in risk of serous invasive cancers, was associated with a modest decrease in risk of endometrioid tumors, and was unassociated with mucinous cancers. Duration of breastfeeding was inversely associated with all 3 subtypes, but the association was strongest for mucinous tumors (RR $= 0.43$ per year). Age at natural menopause was positively associated with the endometrioid subtype only (RR $= 1.13$ per year, 95% CI: 1.04, 1.22). Duration of estrogen use was associated with a strong increase in risk of endometrioid cancers (RR $= 1.87$ per 5-year increase, 95% CI: 1.52, 2.31) and a weaker increase in risk of the other subtypes.

Although not statistically significant, there was some evidence of heterogeneity by subtype for parity, tubal ligation, and hysterectomy; the inverse association for oral contraceptive use was similar across subtypes. A first birth was associated with a borderline significant decrease in risk of serous invasive and endometrioid cancers but was unassociated with mucinous tumors. Each additional birth significantly decreased risk of the endometrioid subtype only (RR $= 0.85$, 95% CI: 0.74, 0.99). In general, tubal ligation and hysterectomy were more strongly inversely associated with endometrioid and mucinous cancers.

In an alternative reproductive model with ovulatory years and duration of menopause, associations with number of ovulatory years (P -heterogeneity $= 0.04$), duration of menopause (P -heterogeneity < 0.001), and duration of breastfeeding (P -heterogeneity $= 0.03$) differed significantly by subtype (Table 3). Each 1-year increase in the number of ovulatory years was associated with a significant 8% increase in risk of serous invasive and endometrioid tumors but only a 3% increase in risk of mucinous tumors.

Building on the final reproductive model, the associations with several nonreproductive exposures appeared to differ by subtype, but only smoking differed significantly (P -heterogeneity $= 0.03$) (Table 4). Past smoking was associated with decreased risk of endometrioid tumors (RR $= 0.59$, 95% CI: 0.39, 0.90), whereas past/current smoking

Table 1. Baseline Characteristics of Epithelial Ovarian Cancer Cases and Noncases Among 108,870 Women in the NHS in 1976 and 112,996 Women in the NHSII in 1989

	NHS					NHSII				
	Noncases (n = 108,073)	All Epithelial (n = 797)	Serous Invasive (n = 451)	Endometrioid (n = 115)	Mucinous ^a (n = 69)	Noncases (n = 112,869)	All Epithelial (n = 127)	Serous Invasive (n = 45)	Endometrioid (n = 24)	Mucinous ^a (n = 17)
Reproductive/hormonal characteristics										
Mean										
Age, years	42	45	45	44	44	35	37	38	36	35
Duration of oral contraceptive use, months ^b	47	44	44	36	38	53	49	39	62	57
Duration of estrogen use, months ^b	34	44	43	75	20	15	0	0	0	0
Parity among parous women, no.	3.1	3.0	3.2	2.9	2.9	2.1	2.0	2.2	1.8	1.8
Duration of breastfeeding, months ^c	6	4	4	4	2	13	8	11	10	7
Ovulatory years, no. ^d	24	27	28	27	27	17	20	21	18	17
Percentage of the population										
Ever used oral contraceptives	48	38	35	38	43	83	85	87	83	82
Parous	94	90	91	82	95	70	63	67	67	53
Tubal ligation	13	8	9	7	10	16	13	18	4	6
Hysterectomy	13	14	18	10	6	4	6	7	8	0
Other characteristics										
Mean										
Body mass index, kg/m ²	24	24	24	24	23	24	26	24	29	24
Physical activity, MET-hours/week ^e	13	14	15	13	9	21	22	25	18	17
Percentage of the population										
Genital talc use >once/week ^f	28	29	29	30	40					
Past smoker	23	27	29	17	26	21	22	23	8	20
Current smoker	33	31	29	33	44	13	12	16	8	13
Family history of breast cancer	6	8	7	12	8	6	13	20	21	7
Family history of ovarian cancer ^g	3	5	6	0	19	2	1	4	0	0

Abbreviations: MET, metabolic equivalent task; NHS, Nurses Health Study; NHSII, Nurses Health Study II.

^a Includes borderline and invasive tumors.^b Among ever users of oral contraceptives or postmenopausal unopposed estrogens; in the NHSII, only 32 women had used unopposed estrogens at baseline.^c Total duration among parous women in 1986 for the NHS and 1993 for the NHSII.^d Current age (if premenopausal) or age at natural menopause minus (age at menarche + duration of oral contraceptive use in years + parity).^e Physical activity from 1986 for the NHS and 1989 for the NHSII; 3 MET-hours is equivalent to walking at an average pace of 2.0–2.9 miles/hour for 1 hour (1 mile = 1.6 km).^f Use among NHS participants only; collected in 1982.^g First collected in 1992 in the NHS and 1993 in the NHSII.

Table 2. Association Between Reproductive/Hormonal Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 108,870 Women in the NHS From 1976 to 2006 and 112,996 Women in the NHSII From 1989 to 2005^a

	All Epithelial (n = 924)		Serous Invasive (n = 496)		Endometrioid (n = 139)		Mucinous (n = 86) ^b		P-Heterogeneity ^c
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Age among women <50 years, (per 1-year increase) ^d	1.11	1.09, 1.14	1.15	1.10, 1.19	1.12	1.06, 1.17	1.06	1.00, 1.12	<0.001
Age among women ≥50 years, (per 1-year increase) ^e	1.02	1.01, 1.04	1.04	1.02, 1.06	0.97	0.94, 1.00	1.00	0.96, 1.04	
Parous ^f	0.71	0.57, 0.89	0.73	0.53, 1.02	0.61	0.37, 1.03	1.17	0.56, 2.47	0.09
Parity among parous women ^f	0.94	0.89, 0.99	1.00	0.94, 1.06	0.85	0.74, 0.99	0.95	0.81, 1.13	
Breastfeeding (per 1-year increase) ^g	0.82	0.74, 0.91	0.84	0.73, 0.96	0.74	0.55, 1.00	0.43	0.25, 0.74	0.03
Oral contraceptive use (per 5-year increase)	0.84	0.75, 0.93	0.78	0.66, 0.91	0.77	0.58, 1.02	0.84	0.60, 1.17	0.91
Tubal ligation	0.68	0.56, 0.84	0.83	0.63, 1.09	0.59	0.34, 1.02	0.50	0.25, 1.01	0.26
Hysterectomy	0.69	0.52, 0.91	0.86	0.61, 1.20	0.68	0.39, 1.17	0.45	0.20, 0.98	0.20
Age at natural menopause (per 1-year increase)	1.03	1.00, 1.05	1.02	0.99, 1.06	1.13	1.04, 1.22	1.01	0.93, 1.10	0.05
Estrogen use (per 5-year increase) ^h	1.37	1.25, 1.50	1.28	1.14, 1.44	1.87	1.52, 2.31	1.31	0.89, 1.93	0.009

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

^a Estimates were adjusted for all variables in the table, plus cohort (NHS or NHSII), menopausal status (postmenopause vs. premenopause/perimenopause), missing data on breastfeeding duration (yes/no) because of noncompletion of questionnaire, and missing age at natural menopause (yes/no) because of hysterectomy prior to menopause.

^b Includes borderline and invasive tumors.

^c P value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

^d RR for each 1-year increase in age prior to age 50 years.

^e RR for each 1-year increase in age at age 50 years or older.

^f Parous: RR for 1 versus 0 children; parity among parous women: RR for each additional child after the first.

^g Breastfeeding duration first collected in 1986 in the NHS and 1993 in the NHSII.

^h Duration of postmenopausal use of unopposed estrogens.

was associated with a nonsignificant increased risk of mucinous cancers. Body mass index was positively associated with the endometrioid subtype (RR = 1.18 per 5 kg/m², 95% CI: 1.02, 1.38) but was unassociated with the other subtypes (P-heterogeneity = 0.06). There also were nonsignificant positive associations between physical activity and serous invasive cancers and between talc use and mucinous tumors. The results for physical activity were unchanged when 1986 was used as the baseline (results not shown).

For the association with all epithelial cancers, the AUC for the reproductive model (AUC = 0.624) was slightly higher than that for the ovulatory years model (AUC = 0.617), indicating that these models have similar discriminatory ability (Table 5). The goodness of fit for the reproductive model was highest for the endometrioid subtype (AUC = 0.714), intermediate for the mucinous subtype (AUC = 0.678), and lowest for the serous invasive subtype (AUC = 0.614). Adding the nonreproductive exposures improved the goodness of fit overall and for each subtype. Although the AUC for each model was based on a slightly different study population, the results were similar when we used the same population for all models (results not shown).

All results were essentially unchanged when we restricted analyses to the NHS only or excluded primary peritoneal

cases (results not shown). In analyses of serous versus non-serous cancers, there were significant differences for the associations with age, parity, tubal ligation, and duration of breastfeeding but no differences for nonreproductive exposures (results not shown). When mucinous cancers were compared with nonmucinous cancers, the associations with only age, duration of breastfeeding, and number of ovulatory years differed significantly (results not shown). When we included clear-cell cancers in the reproductive model, the associations with age, parity, duration of estrogen use, and duration of breastfeeding differed significantly across the 4 subtypes (results not shown).

DISCUSSION

These results suggest that associations with several ovarian cancer risk factors differ by histologic subtype. We observed significant heterogeneity across the serous invasive, endometrioid, and mucinous subtypes for associations with both reproductive and nonreproductive exposures, including age, duration of breastfeeding, duration of estrogen use, and smoking status. There was some evidence of heterogeneity by subtype for several other exposures, including parity and

Table 3. Association Between Ovulatory Years and Other Reproductive/Hormonal Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 107,352 Women in the NHS From 1976 to 2006 and 112,632 Women in the NHSII From 1989 to 2005^{a,b}

	All Epithelial (n = 767)		Serous Invasive (n = 397)		Endometrioid (n = 118)		Mucinous ^c (n = 80)		P-Heterogeneity ^d
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Ovulatory years (per 1-year increase) ^e	1.07	1.05, 1.08	1.08	1.06, 1.10	1.08	1.05, 1.11	1.03	1.00, 1.07	0.04
Duration of menopause (per 1-year increase)	1.02	1.01, 1.04	1.04	1.02, 1.06	0.96	0.93, 0.99	1.00	0.97, 1.04	<0.001
Breastfeeding (per 1-year increase) ^f	0.80	0.71, 0.89	0.85	0.73, 0.98	0.68	0.49, 0.94	0.45	0.27, 0.77	0.03
Tubal ligation	0.69	0.55, 0.85	0.86	0.65, 1.16	0.57	0.32, 1.00	0.51	0.25, 1.04	0.21
Hysterectomy	0.69	0.52, 0.92	0.77	0.53, 1.13	0.78	0.42, 1.44	0.57	0.23, 1.42	0.81
Estrogen use (per 5-year increase) ^g	1.36	1.13, 1.64	1.45	1.16, 1.81	2.33	1.53, 3.53	0.93	0.38, 2.26	0.08

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

^a Estimates were adjusted for all variables in the table, plus cohort (NHS or NHSII), parous (yes/no), menopausal status (postmenopause vs. premenopause/perimenopause), and missing data on breastfeeding duration (yes/no) because of noncompletion of questionnaire.

^b Model excludes women with missing age at natural menopause because of hysterectomy prior to menopause.

^c Includes borderline and invasive tumors.

^d P value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

^e Current age (if premenopausal) or age at natural menopause minus (age at menarche + duration of oral contraceptive use in years + parity).

^f Breastfeeding duration first collected in 1986 in the NHS and 1993 in the NHSII.

^g Duration of postmenopausal use of unopposed estrogens.

body mass index, but these differences were not statistically significant.

Previous epidemiologic studies have reported differences in the risk factors for each histologic subtype of ovarian cancer, although most studies were retrospective and few

reported a statistical test of differences in risk across subtypes. In a pooled analysis, parity and oral contraceptive use were inversely associated with all 4 major subtypes, although parity was most protective for endometrioid and clear-cell tumors, and breastfeeding was inversely

Table 4. Association Between Nonreproductive Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 108,446 Women in the NHS From 1976 to 2006 and 112,054 Women in the NHSII From 1989 to 2005^a

	All Epithelial (n = 876)		Serous Invasive (n = 468)		Endometrioid (n = 134)		Mucinous ^b (n = 84)		P-Heterogeneity ^c
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Body mass index (per 5-kg/m ² increase)	1.05	0.98, 1.12	0.97	0.88, 1.07	1.18	1.02, 1.38	0.90	0.72, 1.13	0.06
Activity (per 15-MET-hour/week increase) ^d	1.05	0.98, 1.13	1.08	0.98, 1.19	0.94	0.76, 1.16	0.82	0.61, 1.10	0.11
Talc use (once/week vs. <once/week) ^e	1.06	0.89, 1.28	1.06	0.84, 1.35	1.06	0.66, 1.69	1.50	0.84, 2.66	0.55
Past smoker	1.05	0.91, 1.22	1.09	0.89, 1.34	0.59	0.39, 0.90	1.54	0.94, 2.53	0.03
Current smoker	1.11	0.92, 1.35	1.14	0.88, 1.49	0.93	0.59, 1.47	1.52	0.85, 2.74	
Family history of breast cancer	1.29	1.07, 1.56	1.34	1.04, 1.73	1.94	1.24, 3.03	1.42	0.76, 2.63	0.38
Family history of ovarian cancer ^f	1.75	1.19, 2.57	1.85	1.13, 3.03	0.47	0.07, 3.39	4.50	1.76, 11.51	0.06

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

^a Estimates were adjusted for all variables in the table, plus all covariates in the final reproductive model (Table 2) and variables for missing data on talc use or family history of ovarian cancer (yes/no).

^b Includes borderline and invasive tumors.

^c P value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

^d Cumulative average physical activity beginning in 1986 for the NHS and 1989 for the NHSII.

^e Information on regular genital talc use available for NHS participants only; collected in 1982.

^f Information on family history of ovarian cancer first collected in 1992 in the NHS and 1993 in the NHSII.

Table 5. AUC for Total Epithelial Ovarian Cancer and Each Histologic Subtype Among Women in the NHS From 1976 to 2006 and the NHSII From 1989 to 2005

Model	All Epithelial		Serous Invasive		Endometrioid		Mucinous ^a	
	No. of Cases	AUC	No. of Cases	AUC	No. of Cases	AUC	No. of Cases	AUC
Reproductive (Table 2)	924	0.624	496	0.614	139	0.714	86	0.678
Ovulatory years (Table 3) ^b	767	0.617	397	0.616	118	0.703	80	0.650
Reproductive + nonreproductive exposures (Table 4)	876	0.645	468	0.644	134	0.748	84	0.744
Ovulatory years + nonreproductive exposures ^{b,c}	731	0.643	378	0.652	114	0.746	78	0.719

Abbreviations: AUC, area under the receiver operating characteristic curve; NHS, Nurses Health Study; NHSII, Nurses Health Study II.

^a Includes borderline and invasive tumors.

^b Excludes women with missing age at natural menopause because of hysterectomy prior to menopause.

^c Results from this model are not shown.

associated with the serous, endometrioid, and mucinous subtypes but was most protective for mucinous cancers (6). These results, as well as the pooled associations for family history, body mass index, and smoking, were consistent with our study (6). Tubal ligation was inversely associated with serous and clear-cell cancers in the pooled analysis (6), but other studies have reported inverse associations for tubal ligation or hysterectomy and risk of endometrioid and/or mucinous tumors (8, 13, 14, 21). Age at menopause was associated with an increased risk of endometrioid tumors in a small study ($n = 41$ endometrioid cases) (22) but not in 2 other studies (7, 23), and estrogen use was more strongly positively associated with endometrioid cancers in some (24–26) but not all (13, 27) previous studies. Three studies of ovulatory years reported a positive association with nonmucinous cancers but no association with the mucinous subtype (9, 10, 14), similar to our study.

Among the nonreproductive exposures, recent physical activity was inversely associated with risk of all 4 histologic subtypes in one study, although the association was statistically significant for serous cancers only (28). Similarly, another study noted inverse associations with risk of serous, endometrioid, and mucinous tumors (29). However, prospective studies, including ours (30), generally have observed null or positive associations (31–33). Several previous studies of genital talc use, including an analysis in the NHS (34), observed a stronger positive association with serous or serous invasive cancers (35–38), although 2 studies reported no difference by subtype (39, 40) and 1 reported a positive association with mucinous tumors (38). Although our results generally are consistent with the existing literature, apparent differences, such as those for talc use, may be due to the limited number of cases of endometrioid or mucinous histology.

At one time, it was believed that the majority of epithelial ovarian cancers, regardless of histology, arose through transformation of the ovarian surface epithelium. However, growing evidence suggests a varied origin of these cancers; for example, high-grade serous carcinomas may arise in the distal fallopian tube (41–43). Morphologically, serous tumors resemble normal fallopian tube epithelium, endometrioid tumors resemble normal endometrium, and mucinous tumors resemble benign intestinal mucosa or cervical epithelium (4).

In addition, there are similarities in gene expression between each subtype and its corresponding normal tissue (5).

The risk factor profiles we observed are consistent with evidence that each subtype resembles a different normal tissue. For example, parity, duration of breastfeeding, and smoking were inversely associated with risk of endometrioid tumors, whereas duration of estrogen use and body mass index were positively associated with risk. This pattern of risk factors is similar to that for endometrial cancer, which is influenced by estrogens and is positively associated with hormone-related exposures, most notably obesity and estrogen use (44). For the mucinous subtype, our results suggest that exposure to carcinogens and other chemicals (e.g., tobacco smoke or talc) may increase risk, whereas surgical procedures that decrease ovarian exposure to exogenous agents (e.g., tubal ligation or hysterectomy) may be protective. Although these results generally are not consistent with known risk factors for colon or cervical cancer (45, 46), evidence exists that smoking (47, 48) and exposure to certain chemicals (49–51) may increase risk of these cancers. The serous invasive subtype was associated with reproductive and hormonal exposures, including parity, duration of oral contraceptive use, and duration of estrogen use. Limited data are available on risk factors for fallopian tube carcinoma, although parity and tubal ligation appear to be protective (52). Information on the epidemiology of serous ovarian tumors may be informative for future research of fallopian tube primary carcinomas.

Strengths of our study include the prospective data with repeated measures for most exposures and the large combined study population. In addition, methods used in this analysis allowed for estimation of separate associations with each subtype simultaneously, as well as formal tests for differences across subtypes.

Although our analysis included a large number of epithelial cases, we had a limited number of cases with certain subtypes (e.g., clear-cell and noninvasive serous cancers). Furthermore, we classified histologic subtype based on a review of pathology reports rather than a central pathology review or immunostaining. Although this categorization likely resulted in some misclassification of histologic subtype, a validation study within the NHS found that histologic subtype based on central pathology review corresponded to

the pathology report for a high percentage of cases (17). The incomplete data for a few exposures, in particular talc use and family history of ovarian cancer, also are weaknesses because the limited data may have influenced the observed associations for these exposures. The association with talc use in our analysis differed from the association in a previous analysis of the NHS cohort (34), possibly because of a greater degree of exposure misclassification over 24 years of follow-up. However, the suggestive positive association with the mucinous subtype may reflect a longer latency period between talc exposure and development of mucinous tumors. Finally, the use of a single summary measure for certain exposures, such as physical activity, also may have limited our ability to detect an association. Additional analyses of different types/intensities of physical activity and risk of each subtype would help clarify this association.

In summary, our study provides additional evidence that associations with several ovarian cancer risk factors differ by histologic subtype and that these differences are consistent with known similarities between each subtype and a corresponding normal tissue. Differences in risk by subtype may help explain variability in the association with certain exposures across study populations, because the observed associations may differ depending on the distribution of the exposure and histologies. Future epidemiologic studies of ovarian cancer therefore should examine the histologic subtypes separately to determine whether heterogeneity in the association exists across subtypes. Analyses not taking into account differences in ovarian cancer risk by histologic subtype could be misleading.

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Exhibit 47

ARTICLE

Perineal Powder Use and Risk of Ovarian Cancer

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- Background** Case-control studies have reported an increased risk of ovarian cancer among talc users; however, the only cohort study to date found no association except for an increase in serous invasive ovarian cancers. The purpose of this analysis was to assess perineal powder use and risk of ovarian cancer prospectively in the Women's Health Initiative Observational Study cohort.
- Methods** Perineal powder use was assessed at baseline by self-report regarding application to genitals, sanitary napkins, or diaphragms and duration of use. The primary outcome was self-reported ovarian cancer centrally adjudicated by physicians. Cox proportional hazard regression was used to estimate risk, adjusting for covariates, including person-time until diagnosis of ovarian cancer ($n = 429$), death, loss to follow-up, or September 17, 2012. All statistical tests were two-sided.
- Results** Among 61 576 postmenopausal women, followed for a mean of 12.4 years without a history of cancer or bilateral oophorectomy, 52.6% reported ever using perineal powder. Ever use of perineal powder (hazard ratio [HR]_{adj} = 1.06, 95% confidence interval [CI] = 0.87 to 1.28) was not associated with risk of ovarian cancer compared with never use. Individually, ever use of powder on the genitals (HR_{adj} = 1.12, 95% CI = 0.92 to 1.36), sanitary napkins (HR_{adj} = 0.95, 95% CI = 0.76 to 1.20), or diaphragms (HR_{adj} = 0.92, 95% CI = 0.68 to 1.23) was not associated with risk of ovarian cancer compared with never use, nor were there associations with increasing durations of use. Estimates did not differ when stratified by age or tubal ligation status.
- Conclusion** Based on our results, perineal powder use does not appear to influence ovarian cancer risk.
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In 2013, it is estimated that there will be 22 240 new cases of ovarian cancer and 14 030 ovarian cancer deaths in the United States (US) alone (1). Since the 1960s, there has been speculation that the use of perineal powder is associated with ovarian cancer. In 2006, the International Agency for Research on Cancer (IARC) reviewed studies examining perineal powder use and ovarian cancer and classified talc as a possible carcinogen (2,3). The proportion of US women ever using talc powder on the perineum was estimated in 2001 to be approximately 40% (4), whereas 52% reported ever use of perineal powder in 1993–1998 within the Women's Health Initiative (WHI) (5).

The primary proposed mechanism linking perineal powder use to ovarian cancer is an inflammatory response (6). Talc particulates from perineal application have been shown to migrate to the ovaries (6), disrupting the surface ovarian epithelial tissue leading to entrapment of the talc particles within inclusion cysts (7). Furthermore, tubal ligation and/or hysterectomy, which would eliminate the pathway of talc particulates to the ovaries, are associated with reduced ovarian cancer risk (6).

A meta-analysis examining the risk of ovarian cancer among ever perineal powder users vs non-users showed odds ratios (ORs)

of 1.40 (95% confidence interval [CI] = 1.29 to 1.52) for population-based case-control, 1.12 (95% CI = 0.92 to 1.36) for hospital based case-control, and 1.35 (95% CI = 1.26 to 1.46) for all case-control studies (2). More recently, a large pooled analysis found that ever use of perineal powder increased epithelial ovarian cancer risk by 24% compared with non-use (OR = 1.24, 95% CI = 1.15 to 1.33) (8). Increased risk was associated with invasive serous, endometrioid, clear cell, and borderline serous subtypes of epithelial ovarian cancer (8). However, when looking at the lifetime number of applications of perineal powder, there was no statistically significant trend for increasing applications, attributed to difficulty in recalling details of frequency and duration of perineal powder use (8).

To date there has only been one prospective study conducted examining perineal powder use and risk of ovarian cancer (9). In the Nurses' Health Study (NHS) cohort, no overall association was found between ever use of perineal powder and epithelial ovarian cancer (relative risk [RR] = 1.09, 95% CI = 0.86 to 1.37) or serous ovarian cancers (RR = 1.26, 95% CI = 0.94 to 1.69) (9). However, there was a 40% (95% CI = 1.02 to 1.91) increase in risk for serous

invasive ovarian cancer with ever perineal powder use, which comprises 86% of serous ovarian cancers in this cohort (9).

Limitations of recall bias and misclassification make it difficult to determine the true relationship between perineal powder (10), a commonly used cosmetic product, and ovarian cancer, a disease with poor survival and few known modifiable risk factors. The prior prospective cohort study, which should not be affected by recall bias, had no information on duration of use limiting interpretation. Here we expand on the available evidence by assessing perineal powder use and risk of ovarian cancer in the Women's Health Initiative Observational Study (WHI-OS). The WHI-OS is a large cohort that collected information on several application areas of perineal powder use and their respective durations of use.

Methods

Study Population

The WHI-OS enrolled 93 676 women from 40 clinical centers across the United States from 1993 to 1998 (11). Women were eligible if they were aged 50 to 79 at enrollment, postmenopausal, and planned to reside in the area for at least three years (11). Women were excluded from the WHI-OS if they were participating in another clinical trial, unlikely to survive three years due to medical conditions, or had conditions that would interfere with study participation (11). Participants completed annual mailed questionnaires to update information on risk factors and outcomes, including ovarian cancer (11). Written informed consent was obtained from participants, and all clinical centers were approved by their respective institutional review boards (11). The current analysis was approved by the University of Massachusetts, Amherst Human Subjects Review Committee.

For this analysis, participants were additionally excluded if they reported a bilateral oophorectomy or an unknown number of ovaries at baseline ($n = 20960$), a history of any cancer at baseline except nonmelanoma skin cancer ($n = 10622$), or were missing exposure or follow up information ($n = 516$). After applying the exclusion criteria, 61 576 participants with 429 adjudicated incident ovarian cancer cases remained.

Exposure Ascertainment

Perineal powder use was assessed via self-report at baseline. Participants were asked, "Have you ever used powder on your private parts (genital areas)?" Those who responded yes further indicated the duration of use with the following possible responses: less than 1 year, 1–4 years, 5–9 years, 10–19 years, or 20 or more years. For persons that reported ever use of a diaphragm, participants were asked, "Did you ever use powder on your diaphragm?" and those who responded yes further indicated duration. The third category evaluated was "Did you ever use powder on a sanitary napkin or pad?" with those responding yes also reporting duration. Each area of application variable was assessed dichotomously and the duration of use, collapsed into fewer categories because of small numbers, was assessed categorically as never, 9 years or less, or 10 or more years. A combined ever perineal powder variable and duration variable for any powder use was created; where ever use was defined as report of ever use of any of the three application categories, never was report of never use for all three categories,

and duration was the maximum duration reported of any single area of application, because we could not exclude the possibility that applications were concurrent. Lastly, all possible combinations of the three application areas were assessed.

Outcome Ascertainment

Ovarian cancer cases were initially self-reported by participants in the WHI-OS on annual questionnaires. Medical records, including hospital discharge summaries and pathology reports, were requested for each self-reported case and adjudicated by a physician at the local Clinical Center and then centrally by the WHI's Clinical Coordinating Center (11).

Covariate Ascertainment

Potential covariates considered included age, race, education, alcohol servings per week, smoking status, metabolic equivalent (MET) hours per week of recreational physical activity, Body Mass Index (BMI), and self-reported family history of ovarian or breast cancer. Reproductive factors considered were age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, history of hysterectomy, history of irregular cycles, history of endometriosis, duration of oral contraceptive use, and duration of postmenopausal hormone use. All covariates were from baseline and were not updated.

Statistical Analysis

To estimate the association between perineal powder use and ovarian cancer, proportional hazard regression models were used. Participants contributed person-time until diagnosis of ovarian cancer, death, loss to follow-up, or September 17, 2012, whichever came first. Participants with other cancers were still considered at risk for ovarian cancer and were not censored at the time of other cancer diagnoses. Information on incident oophorectomy during follow-up was not available and thus participants were not censored in this analysis. The proportional hazards assumption was tested using weighted Schoenfeld residuals.

Covariates were included in the adjusted model according to purposeful selection, where covariates with Wald P values of .25 or less in age-adjusted models were entered into an initial multivariable model and then each covariate was subsequently tested individually via likelihood ratio tests in order of decreasing Wald P values. Variables that had P values of .10 or less during the backwards elimination were kept in the model until a parsimonious model was obtained. Additional variables shown in previous literature (8,9) but not statistically significant in our population were also included in the final multivariable model. Lastly, family history of breast cancer and personal history of endometriosis did not change estimates and were not included in the final multivariable model.

Models fitted included the following independent variables: 1) combined ever perineal powder use, 2) ever powder use by application area (ie, applied to genitals, applied to diaphragm, or applied to sanitary napkins), 3) duration of use by application area, and 4) application area combinations (ie, genital only, diaphragm only, sanitary napkin only, genital and sanitary napkin, genital and diaphragm, diaphragm and sanitary napkin, and all three areas of application). For duration models, test for trend was used to evaluate linear trends across duration categories by modeling the

categories as a continuous variable in the multivariable regression models.

Because powder particles may not reach the ovaries due to tubal ligation and because previous studies have shown a stronger association between powder use and ovarian cancer in women without tubal ligation (4), we separately examined women without tubal ligation. We also stratified by age at baseline, because older women may have had more potential for exposure to talc contaminated with asbestos. Additionally, associations by ovarian cancer histological subtype were evaluated. All analyses were performed using Stata v.12.1 (StataCorp, College Station, TX) and two-sided *P* values of .05 or less were considered statistically significant.

Results

The average age of the participants at baseline was 63.3 years. Participants were followed for a mean of 12.4 years; never powder users were followed for a mean of 12.2 years (range = 0.12 to 17.9 years) and ever powder users were followed for a mean of 12.6 years (range = 0.03 to 18.0). The majority of the participants were white (83.7%), had less than a college degree (56.1%), and were overweight/obese (57.2%). Approximately half (52.6%) of the population reported ever use of perineal powder. Ever powder users were heavier (27.5 kg/m² vs 26.5 kg/m², *P* < .0001) and were more likely to have used oral contraceptives (44% vs 36%, *P* < .0001) and/or diaphragms (50.8% vs 37.3 %, *P* < .0001) than never users (Table 1).

Use of powder on the genitals was associated with a 12% increase in the multivariable-adjusted hazard ratio of ovarian cancer ($HR_{adj} = 1.12$, 95% CI = 0.92 to 1.36), though this was not statistically significant (Table 2). Use of powder on sanitary napkins ($HR_{adj} = 0.95$, 95% CI = 0.76 to 1.20) or diaphragms ($HR_{adj} = 0.92$, 95% CI = 0.68 to 1.23) also was not associated with risk. Duration of powder use on the genitals, sanitary napkins, or on the diaphragm was not associated with ovarian cancer; P_{trend} for years of use: .67, .69, and .67 respectively. Combined ever powder use from any of the three application areas did not show an association with ovarian cancer risk ($HR_{adj} = 1.06$, 95% CI = 0.87 to 1.28). For combined duration of use, which was the longest duration of use among the three areas of application, there was no evidence of an association with risk of ovarian cancer [P_{trend} for years of use: .77]. Use of powder on genitals, the most common application area, for 20 or more years was not associated with increased risk of ovarian cancer compared with never users ($HR_{adj} = 1.10$, 95% CI = 0.82 to 1.48). In a sensitivity analysis, invasive serous ovarian cancer risk was not increased ($HR_{adj} = 0.96$, 95% CI = 0.65 to 1.41), even in women reporting durations of use greater than 10 years.

There was no evidence of an association between perineal powder use and ovarian cancer risk by category of application (Table 3). Combined ever powder use was not associated with individual subtypes of ovarian cancer (Table 4). The multivariable-adjusted hazard ratio for serous ovarian cancer was 1.16 (95% CI = 0.88 to 1.53). Additionally, duration of combined ever powder use was also not shown to be associated with any subtype of ovarian cancer (results not shown).

The associations of combined ever powder use and ovarian cancer did not statistically differ by tubal ligation status (results not shown). When stratified by age group at baseline, hazard estimates also did not statistically differ ($P_{interaction} = .37$); HR_{adj} for younger than

Table 1. Characteristics of postmenopausal women according to perineal powder use status (n = 61 285): Women's Health Initiative Observational Study, 1993–2012

Characteristic, n (%)	Never perineal powder use	Ever perineal powder use
	n = 29 066	n = 32 219
Race		
White	24 006 (82.6)	27 336 (84.8)
Nonwhite	4 991 (17.2)	4 811 (14.9)
Body mass index category, kg/m ²		
<25.0	13 056 (44.9)	12 461 (38.7)
25.0–29.9	9 734 (33.5)	10 799 (33.5)
30.0 +	5 935 (20.4)	8 571 (26.6)
Smoking status		
Never	15 347 (52.8)	15 621 (48.5)
Past	11 481 (39.5)	14 339 (44.5)
Current	1 912 (6.6)	1 881 (5.8)
Duration of oral contraceptive use, y		
Never	17 877 (61.5)	17 954 (55.7)
<5	6 241 (21.5)	7 858 (24.4)
5 to <10	2 528 (8.7)	3 270 (10.2)
10 to <15	1 650 (5.7)	2 125 (6.6)
15+	760 (2.6)	1 005 (3.1)
Diaphragm use	10 826 (37.3)	16 353 (50.8)
Tubal ligation	4 929 (17.0)	5 901 (18.3)
Hysterectomy	6 878 (23.7)	8 285 (25.7)
Family history of ovarian cancer	606 (2.1)	660 (2.1)
Parity		
0	3 687 (12.7)	3 769 (11.7)
1–2	9 773 (33.6)	11 585 (36.0)
3–4	11 101 (38.2)	12 609 (39.1)
5+	4 365 (15.0)	4 098 (12.7)
Age at last birth, y		
Never had term pregnancy	6 219 (21.4)	6 260 (19.4)
< 20	210 (0.7)	324 (1.0)
20–29	9 143 (31.5)	11 480 (35.6)
30+	13 011 (44.8)	13 668 (42.4)
Duration of postmenopausal hormone use, y		
Never	13 381 (46.0)	13 880 (43.1)
<5	6 498 (22.4)	7 546 (23.4)
5 to <10	3 783 (13.0)	4 567 (14.2)
10 to <15	2 688 (9.3)	3 128 (9.7)
15+	2 716 (9.3)	3 097 (9.6)

50 to 59 years = 1.29, 95% CI = 0.91 to 1.82; HR_{adj} for those 60 to 69 years = 0.94, 95% CI = 0.70 to 1.26; and HR_{adj} for those 70 to 79 years = 1.01, 95% CI = 0.68 to 1.48. When restricted to only whites or to those who had never used oral contraceptives, results were again unchanged.

Discussion

In this large prospective study, ever perineal powder use was not associated with ovarian cancer risk, nor was it associated with ovarian cancer when assessed by area of application, duration of use, or ovarian cancer subtype. While many case-control studies have shown an approximately 24–40% increase in risk of ovarian cancer (2,8) for powder users, we did not find evidence of this association in our large, prospective analysis.

The meta-analysis of 20 case-control studies by Langseth and colleagues found a 35% increase in the odds of epithelial ovarian

Table 2. Age and multivariable-adjusted hazard ratios of ovarian cancer by area of perineal powder application (n = 61576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR		Multivariable HR*	
			(95% CI)	<i>P</i> _{trend} †	(95% CI)	<i>P</i> _{trend} †
Powder use on genitals						
Never	247	457 855	1.0 (referent)	.63	1.0 (referent)	.67
Ever‡	181	304 867	1.13 (0.93 to 1.37)		1.12 (0.92 to 1.36)	
Less than 9 years	112	173 118	1.24 (0.99 to 1.55)		1.23 (0.98 to 1.54)	
10 or more years	68	129 647	0.98 (0.75 to 1.29)		0.98 (0.75 to 1.29)	
Powder use on sanitary napkins						
Never	336	590 351	1.0 (referent)	.70	1.0 (referent)	.69
Ever‡	93	172 712	0.96 (0.76 to 1.21)		0.95 (0.76 to 1.20)	
Less than 9 years	62	114 305	0.98 (0.75 to 1.28)		0.96 (0.73 to 1.26)	
10 or more years	30	56 174	0.93 (0.64 to 1.35)		0.95 (0.65 to 1.37)	
Powder use on diaphragm						
Never	373	661 239	1.0 (referent)	.78	1.0 (referent)	.67
Ever‡	52	97 714	0.94 (0.70 to 1.25)		0.92 (0.68 to 1.23)	
Less than 9 years	35	67 468	0.93 (0.66 to 1.32)		0.91 (0.64 to 1.30)	
10 or more years	17	29 202	0.99 (0.61 to 1.60)		0.95 (0.58 to 1.56)	
Combined ever powder use§						
Never	197	361 583	1.0 (referent)	.67	1.0 (referent)	.77
Ever‡	232	404 983	1.07 (0.89 to 1.30)		1.06 (0.87 to 1.28)	
Less than 9 years	135	228 931	1.12 (0.90 to 1.39)		1.09 (0.88 to 1.36)	
10 or more years	97	173 307	1.03 (0.81 to 1.31)		1.02 (0.80 to 1.30)	

* Adjusted for: Age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children, missing).

† Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models; *P*_{trend} was estimated by modeling categories as continuous. All statistical tests were two-sided.

‡ Person-years may not add up; duration information was missing for some.

§ Combined ever powder use is the longest duration of use among the applications to genitals, sanitary napkins, and diaphragms.

Table 3. Age and multivariable-adjusted hazard ratios for ovarian cancer by combined categories of powder use (n = 61576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR*	Multivariable HR*
			(95% CI)	(95% CI)
Powder Type Used				
No powder	193	355 523	1.0 (referent)	1.0 (referent)
Only genital powder	96	158 130	1.14 (0.90 to 1.46)	1.13 (0.88 to 1.45)
Only diaphragm powder	19	42 367	0.82 (0.51 to 1.32)	0.80 (0.50 to 1.29)
Only sanitary napkin powder	28	50 051	1.04 (0.70 to 1.54)	1.01 (0.68 to 1.50)
Genital and sanitary napkin powder	55	96 173	1.09 (0.80 to 1.47)	1.08 (0.80 to 1.46)
Genital and diaphragm powder	24	29 858	1.49 (0.98 to 2.28)	1.45 (0.95 to 2.23)
Diaphragm and sanitary napkin powder	4	6 858	1.06 (0.40 to 2.86)	1.02 (0.38 to 2.74)
Genital, diaphragm, and sanitary napkin powder	5	18 331	0.51 (0.21 to 1.24)	0.50 (0.21 to 1.22)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided.

Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

cancer among ever perineal powder users compared to never-users (2), and the pooled analysis of eight case-control studies by Terry and colleagues found a 24% increase in the same group (8). Langseth and colleagues did not assess dose-response or risk among subtypes of ovarian cancer (2). Terry and colleagues assessed lifetime applications of perineal powder and found no statistically significant trend with increasing lifetime applications (8). This corroborates our results that there was no statistically significant risk with increasing duration

of perineal powder use, though they were able to capture both frequency and duration (8), whereas we only had duration. Terry and colleagues found elevated risks for invasive serous, borderline serous, endometrioid, and clear cell subtypes of ovarian cancer (8), which we did not observe. One potential reason that case-control studies have found slight increases in risk is the potential for an overestimation of the true association due to recall bias, because the participants are aware of their ovarian cancer status when reporting powder

Table 4. Age and multivariable-adjusted hazard ratios for combined ever powder use by subtype of ovarian cancer (n = 61576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR*	Multivariable HR*
			(95% CI)	(95% CI)
Serous†				
Never	87	355 523	1.0 (referent)	1.0 (referent)
Ever	117	404 983	1.18 (0.89 to 1.56)	1.16 (0.88 to 1.53)
Serous Invasive				
Never	80	355 523	1.0 (referent)	1.0 (referent)
Ever	105	404 983	1.16 (0.87 to 1.55)	1.13 (0.84 to 1.51)
Mucinous				
Never	12	355 523	1.0 (referent)	1.0 (referent)
Ever	13	404 983	0.98 (0.44 to 2.14)	1.03 (0.47 to 2.27)
Endometrioid				
Never	13	355 523	1.0 (referent)	1.0 (referent)
Ever	20	404 983	1.39 (0.69 to 2.79)	1.29 (0.64 to 2.61)
Other				
Never	47	355 523	1.0 (referent)	1.0 (referent)
Ever	54	404 983	1.04 (0.71 to 1.54)	1.04 (0.70 to 1.54)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

† Includes borderline cancers.

exposure. The prospective nature of our study would eliminate the potential for recall bias. Additionally, the case-control studies tended to have a younger population than our study, which included both premenopausal and postmenopausal ovarian cancers (2,8), whereas the WHI cohort consisted only of postmenopausal ovarian cancers. Ovarian cancer that occurs prior to menopause may have a different etiology than ovarian cancer occurring afterwards.

We found similar results to that of the NHS, the only other prospective cohort, which had a similar sample size and number of ovarian cancer cases to our study. Ever use of perineal powder did not appear to be associated with ovarian cancer in the NHS (9), similar to our findings. The results of Gertig and colleagues were also null for use on the genitals and for use on sanitary napkins (9). Additionally, neither our study nor the NHS found associations with serous ovarian cancer, endometrioid, or mucinous ovarian cancers, although subgroup sample size may have reduced statistical power to test these associations. In contrast to our results, the study by Gertig and colleagues found a 40% increase in invasive serous ovarian cancer among ever powder users compared with never powder users (9).

Strengths of our study included large sample size with a substantial number of ovarian cancer cases, a prospective cohort design, good case ascertainment, and detailed information on most ovarian cancer risk factors. We also had information on duration of powder use, qualifiers not available in several earlier studies, including the previous cohort study (2,8,9).

One potential limitation of our analyses includes a lack of information regarding oophorectomy after baseline, which would result in the inclusion of some women not at risk for ovarian cancer in the analytical cohort. However, the impact was likely to be minor, as a previous study in the WHI-OS had reported the number of persons with incident bilateral oophorectomies to be less than 250 (out of more than 90 000 participants) during nearly eight years of follow-up (12). While the prospective nature of the study design

eliminates recall bias, it does not eliminate potential for nondifferential misclassification of the exposure. Women still needed to recall past perineal powder use and duration and thus may have trouble recollecting specifics regarding the use of perineal powder, leading to a bias toward the null. Information regarding powder use was not collected after baseline, and there is potential for never users to begin using powder; however, this is unlikely because the women are postmenopausal, reducing need to use perineal powder on diaphragms or sanitary napkins. We also had no specific data regarding the frequency of powder use in our sample. Frequency of use, as well as duration may influence ovarian cancer risk. We may have been comparing long-term infrequent users with short-term frequent users. If we had frequency of use in addition to the duration, we could have looked at intensity of use, which may be more accurate, and shown a dose response relationship. However, Terry and colleagues did not find a dose response relationship either when taking into account frequency and duration (8).

When restricted to women without tubal ligation status, the estimates for the association between combined ever perineal powder use and ovarian cancer were not increased. While some studies have found stronger associations between powder use and ovarian cancer in women that have not undergone a tubal ligation (4), the results from our study did not support this previous finding. The pooled analysis (8) and the NHS cohort (9) also did not find evidence of stronger associations in women without tubal ligations.

While we had information on duration of use, it is unknown during which years the perineal powder was used. Talc powder had potential for asbestos contamination (13) until 1976, when the Cosmetic, Toiletry, and Fragrance Association required all cosmetic talc products to be free of asbestos (14). Therefore, those using powder prior to 1976 may have been potentially exposed to asbestos, a known carcinogen. The pooled analysis and meta-analysis also included case-control studies not within the United States

(2,8), which potentially have different regulations regarding perineal powder and earlier studies that may have been more likely to include exposure to contaminated perineal powder (2). However, risk estimates in more recent studies are similar to earlier studies (2), reducing the likelihood that confounding by asbestos is driving the findings. Additionally, assuming older women in the cohort could have been exposed longer to perineal powder with potential contamination compared with younger women, we did not see statistically significant differences in risk when stratified by age group, further suggesting asbestos contamination is not a likely explanation.

The WHI-OS queried general perineal powder use rather than talc powder use, and we had no specific information regarding the content of talc in products used, which the previous literature reviewed by IARC suggested to be the possible carcinogen of concern (2). However, the NHS cohort and most studies included within the pooled analyses asked about general perineal powder use as well (2,8,9). In summary, perineal powder use did not appear to be associated with ovarian cancer risk in this large sample of postmenopausal women, even with use for long durations.

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Exhibit 48



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Douching, Talc Use, and Risk of Ovarian Cancer

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Abstract

Background—Douching was recently reported to be associated with elevated levels of urinary metabolites of endocrine disrupting phthalates, but there is no literature on douching in relation to ovarian cancer. Numerous case-control studies of genital talc use have reported an increased risk of ovarian cancer, but prospective cohort studies have not uniformly confirmed this association. Behavioral correlation between talc use and douching could produce confounding.

Methods—The Sister Study (2003–2009) enrolled and followed 50,884 women in the US and Puerto Rico who had a sister diagnosed with breast cancer. At baseline participants were asked about douching and talc use during the previous 12 months. During follow-up (median of 6.6 years) 154 participants reported a diagnosis of ovarian cancer. We computed adjusted hazard ratios (HR) and 95% confidence intervals (CI) for ovarian cancer risk using the Cox proportional hazards model.

Results—There was little association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73 CI: 0.44, 1.2). Douching was more common among talc users (OR: 2.1 CI: 2.0, 2.3), and douching at baseline was associated with increased subsequent risk of ovarian cancer (HR: 1.9 CI: 1.2, 2.8).

Conclusions—Douching but not talc use was associated with increased risk of ovarian cancer in the Sister Study.

Keywords

ovarian cancer; talc; douching; phthalates

Introduction

Cancer of the ovary is the most lethal gynecological cancer in women, and its etiologies remain poorly understood. In 2015, there were an estimated 21,290 new cases and 14,180 ovarian cancer deaths among women in the United States (1). Family history of ovarian or breast cancer is a major risk factor. Nulliparity is also associated with increased risk of

ovarian cancer, whereas tubal ligation and oral contraceptive use are reportedly associated with reduced risk (2).

Genital talc use and douching could plausibly introduce particles and toxicants into the upper reproductive tract and increase the risk of cancers and infections. Talc particles have been found embedded in cervical and ovarian tumors (3). Some douching products are known to contain phthalates, which disrupt endocrine pathways and could influence ovarian cancer risk through hormone disruption (4). A recent analysis of data from the National Health and Nutrition Examination Survey found an association between douching and urinary concentrations of phthalates (5). Douching has also been associated with adverse health effects and reproductive problems such as pelvic inflammatory disease and ectopic pregnancy (6), as well as decreased fertility (7).

To the best of our knowledge, no existing studies have investigated the association between douching and ovarian cancer, but talc use was associated with ovarian cancer in many case-control studies (8–13). A meta-analysis of 14 population-based, case-control studies (14) and a large, pooled case-control analysis (15) both reported positive associations between genital talc use (ever vs. never) and ovarian cancer. The only prospective studies to examine talc and ovarian cancer (16, 17) found no strong associations overall, but one observed increased risk for invasive serous ovarian cancer, specifically (17). In this study we investigate the association between ovarian cancer and both douching and talc use, using prospective data from the Sister Study cohort.

Methods

The Sister Study, launched in 2003, enrolled 50,884 women across the United States and Puerto Rico. Enrollees were aged 35 to 74 years and had never had breast cancer but each had a full or half-sister who had been diagnosed with breast cancer. More than one sister per family could participate.

After excluding participants who had bilateral oophorectomies (N=9,023) or ovarian cancer (N=167) prior to enrollment or who had no follow-up information (N=40), we included 41,654 participants in this analysis. As of July 2014 (median follow-up 6.5 years), 154 incident ovarian cancer cases had occurred. We included tumors of the ovary (N=135), fallopian tubes (N=7), peritoneum (N=4), or of uncertain origin but likely from one of the three aforementioned primary sites (N=8). The Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus Group approved this study and all participants provided written consent.

Participants completed computer-assisted telephone interviews, which included questions about reproductive history (including any oophorectomies), health conditions, and lifestyle factors. Participants also completed a self-administered questionnaire about personal care products used in the 12 months prior to enrollment, which included questions about frequency of douching and about genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1–3 times per month, 1–5 times per

week, or more than 5 times per week. Because most members of the cohort reported not douching and not using talc, we used dichotomous use/nonuse variables for analysis.

Updated information on oophorectomies was collected in follow-up questionnaires administered every 2–3 years. We ascertained information on any new cancers via an annual health update and the follow-up questionnaires and were able to confirm 96 of the ovarian cancer cases using medical records (N=87) or death certificate/National Death Index data (N=9). For the remaining 58 cases, we relied on information provided by the participant herself (N=52) or her next of kin (N=6). Among women with available medical records who self-reported ovarian cancer, 90% were confirmed.

There were five eligible cases with an unknown exact age at diagnosis. For them, we imputed an age midway between their last ovarian cancer-free follow-up interview and their age at the time we were notified of the diagnosis (or death). Although we did not genotype women directly for *BRCA1* or *BRCA2* mutations, we asked each woman in her baseline interview whether she had ever been tested and, if so, what the result of those tests were. For the purposes of this analysis, a woman was treated as *BRCA1/2* mutation positive if 1) she had a positive test or 2) she had a sister with a known positive test and she had no known negative test.

Statistical Analyses

We computed adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association of talc use and douching with ovarian cancer risk using Cox proportional hazards models, with age as the primary time scale. Follow-up lasted from age at baseline until age at diagnosis of ovarian cancer. Follow-up time was censored at their age of bilateral oophorectomy after baseline, death, or last contact. Because some participants had sisters who also enrolled in the cohort, we used generalized estimating equation methods to calculate robust variances to account for family clustering. We evaluated proportionality assumptions of the Cox model by assessing the improvement in goodness-of-fit provided by including an age-by-factor interaction term.

In addition to the main effect, we evaluated the joint effect of both douching and using talc. We classified participants into four categories: neither exposure, talc use exclusively, douching exclusively, or both exposures. We also carried out a number of stratified analyses. We stratified by reproductive factors such as menopausal status, parity, hysterectomy, and tubal ligation to explore possible effect modification (10, 13). We tested for differences across strata using the p-value for an exposure-by-modifier interaction term.

We selected potential confounders or effect modifiers of the association between ovarian cancer and the exposures of interest in this analysis *a priori* based on assumed causal relationships among the covariates (18), and included: patency (yes/no blockage of reproductive tract by tubal ligation or hysterectomy), menopausal status (pre- or postmenopausal), duration of oral contraceptive use (none, <2 years, 2–<10 years, 10 or more years), parity (yes/no), race (non-Hispanic white, non-Hispanic black, Hispanic or other), and body mass index (BMI; <25, 25–29.9, or >30 kg/m²), all of which were fixed at baseline levels.

We conducted six sensitivity analyses. In the first, we restricted to the 96 cases confirmed by medical record or death certificate/National Death Index data. For our second sensitivity analysis we looked for evidence of etiologic heterogeneity by further restricting this pool to medically confirmed cases with serous ovarian cancer (N=49). For our third sensitivity analysis, we included all 154 eligible ovarian cancer cases as well as 5 additional cases that had unknown ages at diagnosis and pre-baseline oophorectomies (N=159 cases total). We did this to examine the influence of our assumptions about the relative timing of their oophorectomies versus their ovarian cancer diagnoses. We further examined the influence of imputing age at diagnosis in our fourth sensitivity analysis by excluding the 5 cases with imputed diagnosis ages but intact ovaries (N=149 cases total). For our fifth sensitivity analysis, we excluded participants from families known to carry *BRCA* mutations (N=347 exclusions, including 10 cases) since the lifetime risk of ovarian cancer for individuals with a *BRCA1/2* mutation is substantially higher (19) and the etiology may be different. Lastly, we conducted analyses excluding the first year of follow-up, to minimize the possibility that symptoms of undiagnosed ovarian cancer were leading participants to use douche or talc. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and using the Sister Study data release version 4.1.

Results

Table 1 summarizes characteristics of cases and non-cases at baseline. Most participants were non-Hispanic white (84%), and most were postmenopausal (56%). Women who later became cases were somewhat older (mean 57.8 versus 54.8), more often white, and more often nulliparous. Cases were also more likely to have a first-degree family history of ovarian cancer and more than one first-degree relative with breast cancer. They were also more likely to carry a deleterious mutation in *BRCA1* or *BRCA2*. While ever/never use of oral contraceptive was similar across cases and non-cases, the distribution of duration of use differed. More non-cases (26%) than cases (16%) had used oral contraceptive for more than 10 years. Compared to women who neither douched nor used talc, women who douched were more likely to be non-Hispanic black (23% vs. 6%) and to have less than a college degree (62% vs. 44%) and women who used talc were more likely to have a BMI over 30 kg/m² (41% vs. 25%; eTable).

Douching in the 12 months prior to study enrollment was reported by 13% of non-cases and 20% of cases (Table 2). Talc use in the 12 months prior to study enrollment was reported by 14% of non-cases and 12% of cases. Only 7 cases (5%) reported both douching and talc use.

Ever douching during the 12 months prior to study entry was associated with increased ovarian cancer risk (adjusted HR: 1.8, 95% CI: 1.2, 2.8; Table 2). By contrast, talc use during the 12 months prior to study entry was associated with reduced risk after the same confounder adjustments (HR: 0.73 CI: 0.44, 1.2) and there was a negligible change in the estimated effect with additional adjustment for douching (HR: 0.70 CI: 0.42, 1.1). We observed no proportional hazards assumption violations for any of the examined models.

Douching with no talc use was also associated with increased risk of ovarian cancer compared with use of neither talc nor douching (adjusted HR: 1.9 CI: 1.2, 2.9), which is

similar to the overall effect estimate of douching. There was an inverse association between exclusive talc use and ovarian cancer, and a positive association for douching and talc use combined (HR: 1.8, CI: 0.81, 3.9). There was no evidence for interaction on a multiplicative ($p=0.39$) or additive ($p=0.72$) scale.

To explore effect modification, we performed analyses stratified by a number of reproductive factors including tubal ligation status, hysterectomy status, menopause status, and parity (Figure). We also stratified by patency to see if blockage of access to the ovaries by either tubal ligation or hysterectomy might modify the association between ovarian cancer and douching or talc use. For all stratifications, there were no modifications of effect estimates for either douching or talc use (all heterogeneity p -values >0.05).

HRs for talc use differed little in the first five sensitivity analyses, showing a HR change no greater than 0.04. By contrast, exclusion of ovarian cancers without medical record or death certificate confirmation (by censoring their follow-up at the reported diagnosis age) attenuated the association between douching and ovarian cancer (HR: 1.1, CI: 0.62, 2.1). Likewise, restriction to medically confirmed serous ovarian cancer also attenuated effect estimates (HR: 1.4 CI: 0.64, 3.2). However, ovarian cancer cases who had reported that they douched were substantially less likely to have a medical record available (40%) than ovarian cases who did not douche (69%), suggesting that medical records were informatively missing, biasing results based on the restricted analysis. There was very little change in douching effect estimates when excluding the five cases with uncertain diagnosis dates or including the five women reporting oophorectomies before the diagnosis of ovarian cancer. Exclusion of known positive *BRCA1/2* families slightly strengthened the association between douching and ovarian cancer (HR: 1.9, CI: 1.3, 2.9). In our sixth sensitivity analysis, exclusion of the first year of follow-up time resulted in negligible changes in the HRs for douching and talc use (HR: 1.8, CI: 1.2, 2.8 and HR: 0.86, CI: 0.52, 1.4 respectively).

Discussion

In this large prospective cohort, which gave rise to 154 incident cases of ovarian cancer, there was a positive association between douching and incident ovarian cancer. Talc use was associated with a slight reduction of ovarian cancer risk. Our study of ovarian cancer grouped together all cancers designated as ovarian (88%), fallopian (5%), peritoneal (3%), or those designated as uncertain but either ovarian, fallopian, or peritoneal (5%). With recent literature suggesting that most cancers classified as ovarian likely originated in the fallopian tubes (20), we felt that this grouping was appropriate.

Interest in talc as a carcinogen arose because of its chemical similarity to asbestos, which has been previously linked to ovarian cancer (21). One challenge with studying talc is that the chemical formulation of talc has changed over time (9), and not all powders contain the mineral talc (e.g. cornstarch-based products). Previous case-control studies have noted evidence for a positive association (8–13), with some evidence that the effect is strongest in premenopausal women (13). Given these results, the biological plausibility, the rarity of the exposure, and imprecision of estimates, we cannot exclude a small increase in risk

associated with talc use, despite our inverse findings. Then again, with the exception of the finding that talc use was positively associated with serous ovarian cancer in the Nurses' Health Study (17), the prospective studies have not provided evidence supporting an association between talc use and ovarian cancer overall (17) or between talc use and ovarian cancer overall among post-menopausal women (16).

The numbers for the Sister Study as a whole given in Table 2 reveal an odds ratio of 2.1 (CI: 2.0, 2.3) for douching in relation to talc use. Thus, the two practices are correlated. If douching is a risk factor for ovarian cancer, some of the earlier reports on talc could have been subject to confounding bias. However, the one case-control study that did include douching as a covariate still observed a positive association between talc use and ovarian cancer risk (8). Another factor that may contribute to our null findings is that we categorized the exposure based on the 12 months prior to enrollment as a dichotomous ever/never factor rather than a quantitative measure of total applications, as has been done in previous studies.

Because Sister Study participants all have a first-degree family history of breast cancer, they are more likely than the general population to develop ovarian cancer (estimated observed/expected number of cases = 1.6 based on SEER rates). We also note that, by design, we excluded women with a previous history of breast cancer, thereby discounting some individuals who were at increased risk for ovarian cancer. While these selective factors may limit generalizability, there is no clear mechanism by which they would bias the estimated effect of talc use or douching on ovarian cancer.

Our review of the literature suggests that our study is the first to examine the association between douching and ovarian cancer. This association could reflect uncontrolled confounding by behavioral factors we have not captured well. For example, women may be more likely to douche if they are prone to infections or other reproductive health problems that could themselves be related to ovarian cancer.

If the association is causal, it could be related to the recently reported positive association between douching and higher urinary levels of phthalate metabolites observed in National Health and Nutrition Examination Survey participants (5). Phthalates are endocrine-disrupting chemicals and may be harmful to the fallopian tubes or the ovaries (22). In an animal study, exposure to di-(2-ethylhexyl) phthalate at 500 and 2,000 mg/kg demonstrated ovarian toxicity through decreased progesterone and increased apoptosis in granulosa cells (23). Further, ovarian cancer cell lines have been found to increase cell proliferation and to up-regulate cell-cycle regulatory genes following treatment with di-n-butyl phthalate (24). We did not collect detailed information about specific products used in douching, so we are unable to estimate exposure to individual phthalates.

Douching could also force tissue, menstrual fluids, or foreign materials up the reproductive tract, resulting in inflammation (e.g. pelvic inflammatory disease (6)) or infection of the fallopian tubes or ovaries themselves. This inflammation and infection could also contribute to ovarian cancer risk, as supported by the observed positive association between pelvic inflammatory disease and ovarian cancer (25).

If the association is causal and related to the transfer of xenobiotics into the upper reproductive tract, we would expect to see a stronger association in women with both a uterus and patent fallopian tubes. However, the evidence in our data appeared to be driven by the subcohort of women with hysterectomy and/or tubal ligation (Figure).

Since our study was prospective in nature, it is robust to potential differential reporting bias as exposures are recorded prior to development of cancer. Another important strength of the study was that we controlled for many potentially confounding factors.

An important limitation of our study is that we collected douching and talc information on individuals for the year prior to study entry and have not accounted for the latency of ovarian cancer, which is likely to be long (26). If latency is 15 to 20 years, douching habits at baseline do not accurately reflect the period of risk, although women who douched at baseline are likely to have been douching for a substantial amount of time before that as well. Also, given that there have been health advisories against douching because of its other potential risks, participants who douched in the past may have stopped douching and would be misclassified. Thus, the relative risk for douching in relation to ovarian cancer could be underestimated. Future studies that ascertain a complete history of douching are warranted.

Although the baseline questionnaire did ask women about their use of douche and talc between the ages 10 and 13, very few women responded yes to douching (2%), and we were unable to make use of those data. By contrast, talc use during ages 10–13 had a prevalence of 18% in the cohort, but there was no detectable effect of pre-pubertal talc use on risk (HR: 1.1 CI: 0.74, 1.7).

Exposure information was very complete, with only 832 participants (2%) missing the personal care products questionnaire entirely, and an additional 655 and 1,188 missing data for the questions about douching or talc use, respectively. However, for approximately 37% of cases we have not yet received medical records to confirm the diagnosis. We found that medical record retrieval was differential by exposure, with a lower proportion with medical records among women who douched than among women who did not. This informative missingness mathematically contributed to the substantial attenuation in the HR estimate for the association between vaginal douching and ovarian cancer when we restricted to cases with medical record confirmation. Medical record retrieval for ovarian cancer began only recently, and women with cancers diagnosed early in follow-up are more likely to be missing medical record information. Some of the unconfirmed diagnoses may be confirmed later via medical records or the National Death Index.

In this large, prospective study, we did not observe an association between recent talc use and ovarian cancer risk, but did find a strong positive association between douching and ovarian cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

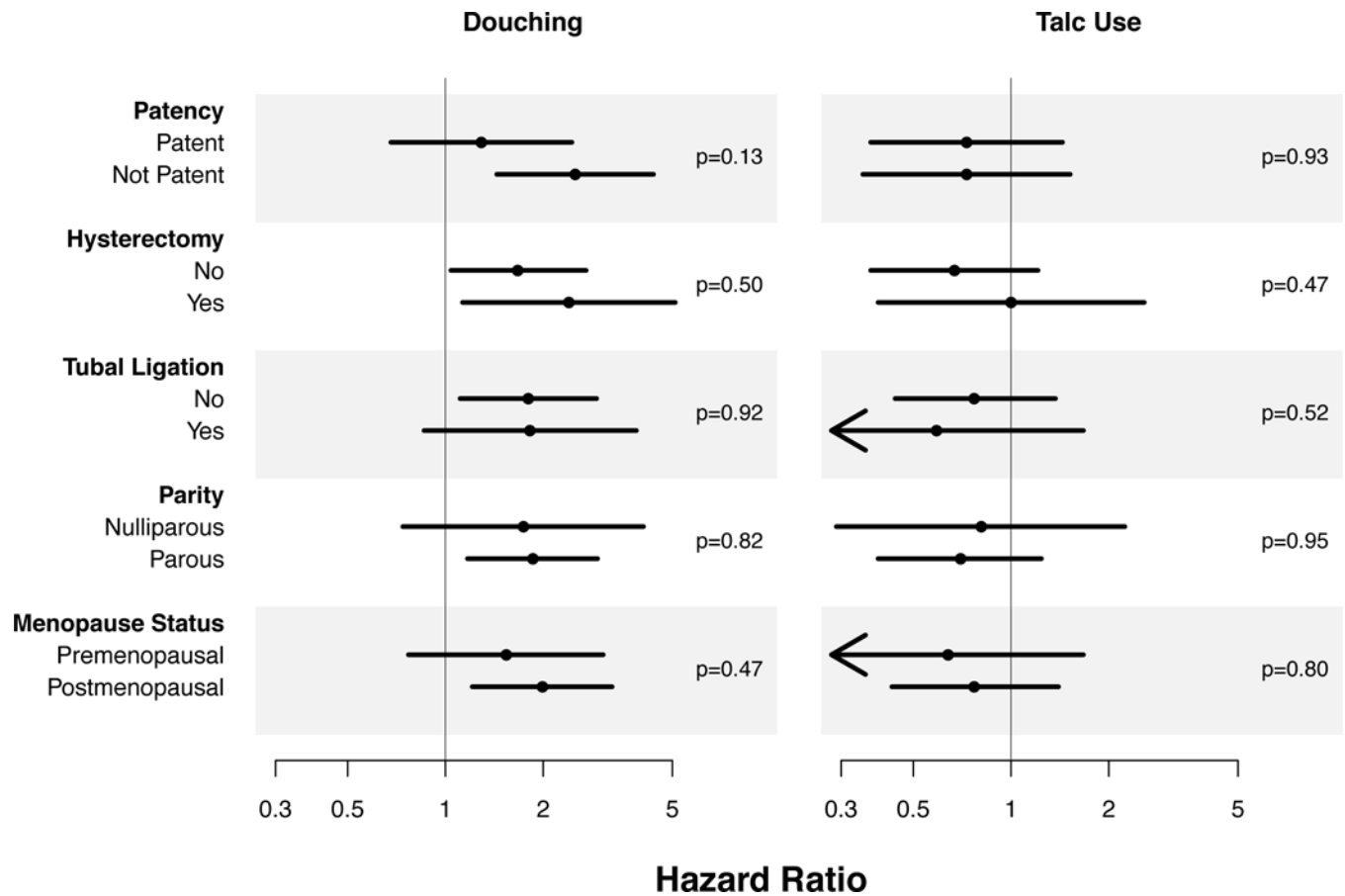
Abbreviations

BMI	body mass index
CI	confidence interval
HR	hazard ratio

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**Figure.**

Effect estimates of douching and talc use in the Sister Study when stratified by multiple reproductive factor, adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency. The reported heterogeneity p-values are for tests of an exposure-by-modifier interaction term.

TABLE 1Baseline characteristics of the Sister Study cohort (2003–2009)^a

	Non-Cases (N=41,500)	Ovarian Cancer Cases (N=154)
Race; N (%)		
Non-Hispanic White	34,745 (84)	138 (90)
Non-Hispanic Black	3,598 (9)	9 (6)
Hispanic	2,076 (5)	5 (3)
Other	1,068 (2)	2 (1)
Education; N (%)		
High school or less	6,001 (14)	24 (15)
Some college	13,556 (33)	49 (32)
Bachelor's degree	11,579 (28)	46 (30)
Graduate degree	10,354 (25)	35 (23)
BMI; N (%)		
<25.0 kg/m ²	16,610 (40)	51 (33)
25–29.9 kg/m ²	13,012 (31)	51 (33)
≥ 30 kg/m ²	11,866 (29)	52 (34)
Menopausal Status; N (%)		
Premenopausal	15,238 (37)	40 (26)
Hysterectomy with ovaries retained	2,996 (7)	8 (5)
Postmenopausal	23,239 (56)	106 (69)
Hysterectomy; N (%)		
No	34,481 (83)	120 (78)
Yes	6,995 (17)	34 (22)
Tubal Ligation; N (%)		
No	29,511 (71)	115 (75)
Yes	11,973 (29)	39 (25)
Oral Contraception		
Duration of Use; N (%)		
None	6,452 (16)	25 (16)
<2 years	6,382 (15)	37 (24)
2–10 years	17,769 (43)	67 (44)
10 years or more	10,865 (26)	25 (16)
Parity; N (%)		
No live births	7,657 (18)	37 (24)
1 or more live births	33,816 (82)	116 (76)
First Degree Family History of		
Ovarian Cancer; N (%)		
No	40,149 (97)	138 (90)
>1 first-degree relative	1,322 (3)	16 (10)
Breast Cancer; N (%)		

	Non-Cases (N=41,500)	Ovarian Cancer Cases (N=154)
1 affected sister	31,291 (75)	109 (71)
>1 sister or sister+mom	10,207 (25)	45 (29)
BRCA1/2 mutation status; N (%)		
No known mutation	41,163 (99)	144 (94)
Known mutation	337 (1)	10 (6)

Missing values: Race (13 non-cases), education (10 non-cases), BMI (12 non-cases), menopausal status (27 non-cases), tubal ligation (16 non-cases), hysterectomy (24 non-cases), oral contraception use (32 non-cases), parity (1 case, 27 non-cases), ovarian cancer family history (29 non-cases), breast cancer family history (2 non-cases).

^aExcludes women who were diagnosed with ovarian cancer before completion of the baseline interview (N=167), women who had a bilateral oophorectomy before the baseline interview (N=9,005), and women lost to follow-up (N=40).

TABLE 2

Exposure prevalence and hazard ratios for their associations with ovarian cancer in the Sister Study

	Non-cases N=41,500	Ovarian cases N=154	Fully Adjusted Hazard Ratio^a
Douching past 12 months			
No	34,653 (87)	121 (80)	1.00
Yes	5,364 (13)	30 (20)	1.84 (1.2, 2.8)
Talc use past 12 months			
No	33,770 (86)	130 (88)	1.00
Yes	5,718 (14)	17 (12)	0.73 (0.44, 1.2)
Douched and used talcum powder past 12 months			
Neither	29,596 (76)	106 (72)	1.00
Talc use/no douching	4,399 (11)	10 (7)	0.60 (0.31, 1.1)
Douching/no talc use	3,936 (10)	23 (16)	1.9 (1.2, 2.9)
Both	1,237 (3)	7 (5)	1.8 (0.81, 3.9)

Missing values: Douching (3 cases, 1,483 non-cases), talc use (7 cases, 2,012 non-cases)

Adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency.

^a Adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency. The reported heterogeneity p-values are for tests of an exposure by modifier interaction term.

Exhibit 49

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A META-ANALYTICAL APPROACH EXAMINING THE POTENTIAL RELATIONSHIP BETWEEN TALC EXPOSURE AND OVARIAN CANCER

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The concern that use of talc or talc-containing substances in the perineal region of women may subject them to an increased risk for ovarian cancer has become an important issue in the study of ovarian cancer. The purpose of this paper is to examine whether this concern, heightened by several epidemiological studies purporting to show an increased risk, is valid. Epidemiological studies examining the possibility of this relationship are reviewed, and meta-analyses of their results are performed. The conclusion reached herein is that the evidence regarding the risk of ovarian cancer associated with talc exposure is equivocal, and further examination of the relationship is required before a sound conclusion can be made.

INTRODUCTION

There has been recent concern that women's use of talc or talc-containing substances in their perineal region puts them at an increased risk for ovarian cancer. This concern has been brought to the forefront by several case-control studies assessing the risk of ovarian cancer associated with perineal talc use. The purpose of this paper is to review, summarize, and pool these studies in order to document any possible association between an increased risk of ovarian cancer and perineal talc use.

Initially, studies were identified using the MEDLINE database and keying on the terms "ovarian cancer" and "talc or cosmetic." Other studies were identified from the references of these studies. To our knowledge the following ten articles are all the published epidemiological studies that address the purported association between talc use and an increased risk of ovarian cancer: Cramer et al. (1982); Harte et al. (1983); Whittemore et al. (1988); Booth et al. (1989); Harlow and Weiss (1989); Chen et al. (1992); Harlow et al. (1992); Rosenblatt et al. (1992); Hankinson et al. (1993); and Tzonou et al. (1993). Hankinson et al. (1993) describe a prospective study; the other nine papers describe case-control studies. Table 1 shows the frequency distributions, type of controls, matching factors

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2. Abbreviations: CI, confidence interval; RR, relative risk.

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TABLE 1. Sample Sizes and Characteristics for the Case-Control Studies

Study	Exposed	Unexposed	Type of Controls	Matching Factors for Controls	Location	Type of tumor
GRAM N = 430	Cases 92 Controls 61	123 154	Population	Precinct of residence, race, and age	Boston, MA	Malignant and borderline
HART N = 293	Cases 54 Controls 78	77 84	Hospital	Age, race, and hospital frequencies (unmatched)	Washington, DC	Malignant
WHIT N = 726	Cases 84 Controls 219	103 320	Hospital and population	Age, race, hospital, and date of admission	San Francisco, CA	Malignant
BOOT N = 651	Cases 141 Controls 256	76 178	Hospital	Age-frequency (unmatched)	London and Oxford, England	Malignant
HAR1 N = 274	Cases 49 Controls 64	67 94	Population	Age and county of residence frequencies (unmatched)	Seattle, WA	Borderline
HAR2 N = 474	Cases 114 Controls 94	121 145	Population	Precinct of residence, age, and race	Boston, MA	Malignant
ROSE N = 122	Cases 67 Controls 10	40 5	Hospital	Race and date of diagnostic admission (<i>a posteriori</i>); two cases per control	Baltimore, MD	Malignant
CHEN N = 336	Cases 7 Controls 5	105 219	Population	Neighborhood and age	Beijing, China	Malignant
TZON N = 389	Cases 6 Controls 7	183 193	Hospital visitors	Hospital ward	Athens, Greece	Malignant

for controls, location, and tumor type considered for the case-control studies. Table 2 shows the crude and adjusted relative risks (RR) and confidence intervals (CI) for the case-control studies.

TABLE 2. Relative Risks for the Case-Control Studies

Study	Crude RR (95% CI)	Adjusted RR (95% CI)	Adjusting Factors
CRAM	1.89 (1.27–2.82)	1.61 (1.04–2.49)	Religion, marital status, education, ponderal index, age at menarche, parity, oral contraceptive or menopausal hormone use, and smoking
HART	0.76 (0.47–1.20)	0.7 (0.4–1.1)	Race, age, and gravidity
WHIT	1.19 (0.85–1.66)	1.40 (0.98–1.98)	Parity
BOOT	1.29 (0.92–1.81)	none available	
HAR1	1.07 (0.66–1.75)	1.1 (0.7–2.1)	Age, parity, and use of oral contraceptives
HAR2	1.45 (1.01–2.09)	1.5 (1.0–2.1)	Parity, education, marital status, religion, use of sanitary napkins, douching, age, and weight
ROSE	0.84 (0.27–2.63)	none available	
CHEN	2.92 (0.81–10.88)	3.9 (0.9–10.6)	Education and parity
TZON	0.90 (0.30–2.74)	1.05 (0.28–3.98)	Age, education, weight, age at menarche, menopausal status and age at menopause, parity and age at first birth, smoking, coffee drinking, alcohol consumption, hair dyeing, use of analgesics, use of tranquilizers, and mutual confounding influences

REVIEW OF THE EPIDEMIOLOGICAL STUDIES

In order to describe the ten epidemiological studies, the following abbreviations for the individual studies are used: CRAM — Cramer et al. (1982), HART — Hartge et al. (1983), WHIT — Whittemore et al. (1988), BOOT — Booth et al. (1989), HAR1 — Harlow and Weiss (1989), HAR2 — Harlow et al. (1992), ROSE — Rosenblatt et al. (1992), HANK — Hankinson et al. (1992), CHEN — Chen et al. (1992), and TZON — Tzonou et al. (1993). Each study is summarized according to the following outline: objective, methods, results, and conclusions.

While case-control studies generally produce odds ratios, not relative risks, the purpose of the odds ratio is to estimate the relative risk. Therefore, in this paper the odds ratios are referred to as relative risks; the reader should remember that the values are actually just estimates of the true relative risks.

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1. CRAM

Objective. To study whether there is an association between exposure to certain hydrous magnesium silicates, such as talc and asbestos, and the incidence of ovarian cancer.

Methods. Originally, 297 cases were thought to be eligible, among whom 215 cases were ultimately selected to participate. The study was restricted to English-speaking residents of Massachusetts whose ages varied between 18 and 80 at the study's inception. The selected 215 cases were all Caucasians with epithelial cancers, including 39 with tumors of borderline malignancy. Population-based matched controls were randomly selected. The final control group consisted of 215 women out of a potential of 475 controls. Stratification and conditional logistic regression were used to accommodate confounders.

Results. Overall, 42.8% of cases and 28.4% of controls reported exposure to talc via direct application to the perineum, by dusting sanitary napkins with talc, or both. The crude relative risk of ovarian cancer for women with any perineal exposure as opposed to women with no perineal exposure was 1.89 (95% CI 1.27–2.82). Women who used talc on both the perineum and sanitary napkins had an adjusted relative risk of 3.28 (95% CI 1.68–6.42). Finally, the adjusted relative risk for women with any exposure was 1.61 (95% CI 1.04–2.49).

Conclusions. The study provides some support for an association between talc and ovarian cancer, hypothesized because of the similarity of ovarian cancer to mesotheliomas and the chemical relation of talc to asbestos, a known cause of mesotheliomas. While this study made a thorough investigation of the association between perineal talc use and an increased risk of epithelial ovarian cancer, some study weaknesses that preclude the existence of a causal relationship are that no dose-response or duration data were reported, and while a major strength of the study is the use of neighborhood controls, this strength is somewhat tempered by the high nonparticipation rate among controls (260/475 = 55%).

2. HART

Objective. To investigate further the association between talc use and the risk of ovarian cancer.

Methods. Originally, there were 197 cases of women with pathologically confirmed primary epithelial ovarian cancer and 197 hospital controls. These controls had conditions that were not gynecological in nature. Psychiatrically disturbed women, pregnant women, and women with other malignancies were also excluded. The controls were frequency-matched on age, race, and hospital. Information on talc use was obtained on 135 cases and 171 controls.

Results. In the group of women in which no use of talc was mentioned versus the group of women in whom any talc was mentioned, constituting the unexposed and exposed groups respectively, the unadjusted relative risk of ovarian cancer for the exposed to the unexposed groups was 0.76 (95% CI 0.47–1.20). Hence, the hypothesis of no association cannot be

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rejected. Further breakdown of the data indicated that only those women who used diaphragms, as opposed to women who did not use diaphragms, showed an elevated relative risk of ovarian cancer of 1.8 (95% CI 0.7–3.7).

Conclusions. The data do not indicate any association between talc use and risk of ovarian cancer. Furthermore, no dose-response data were given, and no attempt was made to control for potential confounding variables other than the matched variables, age and race, and gravidity. Consequently, little evidence of any association between any reported exposure to talc and an increased risk of ovarian cancer is provided. Finally, it is difficult to evaluate the study on the basis of a one-page report. Factors such as smoking status, weight, and marital status are not addressed in this report.

3. WHIT

Objective. To investigate the roles of blood-borne environmental exposures in ovarian cancer risk, the lifetime consumptions of coffee, tobacco, and alcohol were the principal factors of concern in this case-control study. Furthermore, vaginal exposures to talc and other particulates may present an etiologic hypothesis for the occurrence of epithelial cancer. Thus, the purpose of this study was to investigate these possibilities.

Methods. Women diagnosed with ovarian cancer in the San Francisco Bay Area between 1983 and 1985 and ranging in age from 18 to 74 years provided 188 cases for this study. Matched controls from two control groups, hospital controls and population controls, provided a total of 539 controls. The 280 hospital controls were selected from the same hospitals as the cases, whereas the 259 population controls were selected using random digit dialing. All controls were matched to cases on age, race, and having at least one ovary. Further, hospital controls were excluded if they were admitted for psychiatric, obstetric, gynecological, or malignant conditions. Conditional logistic regression was used to adjust the analysis for confounders.

Results. While this study was designed to examine other potential risk factors, i.e., coffee, tobacco, and alcohol, as well as talc exposure in relation to ovarian cancer, the study did not find evidence of an association between genital talc exposure and an increased risk of ovarian cancer. Women who reported regular use of talc on the perineum showed a marginally significant increase in relative risk, but no other differences were noted between cases and controls when considering other types of perineal talc exposure either alone or taken in combination. The crude relative risk of ovarian cancer for women with any perineal exposure, as opposed to women with no perineal exposure, was 1.19 (95% CI 0.85–1.66). Adjusted for parity, the relative risk became 1.40 (95% CI 0.98–1.99). Other calculated relative risks failed to produce any significant associations.

Conclusions. The study neither indicts nor exonerates talc as a potential ovarian carcinogen. However, several sources of bias were mentioned. These include (1) failure to interview all

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eligible ovarian cancer cases and a completely random sample of controls, (2) the potential pitfalls in combining hospital and population controls, (3) random error in reported talc use that tends to attenuate relative risk estimates, and (4) confounding by differential talc use among women with characteristics predictive of ovarian cancer. This last concern is a very important possible confounder that may be difficult to factor out in any future case-control study. If this issue is to be addressed, then a prospective cohort study should be designed that measures hormone levels at baseline; to our knowledge, however, no such study is underway.

4. BOOT

Objective. To study via case-control methodology the various potential risk factors for ovarian cancer, which include infertility, oral contraceptive use, parity, age at menopause, and genital talc use.

Methods. Women with a diagnosis of ovarian cancer were each age-matched to two hospital controls at 13 hospitals in London and two in Oxford, England. For 63 cases recruited from a London hospital where only cancer patients are treated, controls were selected from other London hospitals. The age range for study subjects was 16–65 years. Excluded from the control group were women with bilateral oophorectomy, as well as women with conditions related to reproductive history or oral contraceptive use. All relative risk estimates were adjusted for age in five-year strata and for social class in six categories. A final total of 235 cases and 451 controls was included in the analysis. Maximum likelihood estimates of relative risk with the corresponding 95% confidence intervals were obtained. Tests for trend were computed by means of logistic regression.

Results. Women using talc weekly showed a higher relative risk for ovarian cancer, 2.0 (95% CI 1.3–3.4), than women using talc on a daily basis, $RR = 1.3$ (95% CI 0.8–1.9). If a trend is operative, then such a reversal is, indeed, curious. Furthermore, there was no significant difference between the percentages of cases and controls who used and kept their diaphragms in talc. The crude relative risk of ovarian cancer for women with any perineal exposure versus those women with no exposure was 1.29 (95% CI 0.92–1.81).

Conclusions. The evidence linking talc use with an increased risk of ovarian cancer remains controversial. While it is true that women who used talc weekly or daily had an increased risk compared to women who used talc less frequently, the reversal between weekly and daily use is unexplained, as is the overall nonsignificant relative risk for women with any perineal exposure, compared to women with no exposure. Overall, the study does not provide a clear indication that perineal use of talc increases the risk of ovarian cancer. The authors indicate a possible selective recall bias, in that women were not asked the length of time of their talc use. It may have been that either a woman's symptoms or her disease-related pelvic examinations led her to recall, selectively, her past frequency of talc use.

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5. HAR1

Objective. To investigate whether perineal application of powder, particularly talc, is associated with an increased risk of serious and mucinous borderline ovarian tumors.

Methods. Women residents of three urban, western Washington state counties, diagnosed as having a serious or mucinous borderline ovarian tumor, were identified from the files of the corresponding population-based cancer reporting system. Cases included Caucasian women whose ages were between 20 and 79 and who were diagnosed during the years 1980–1985. Controls were population-based controls located through random digit dialing. Women who had bilateral oophorectomy were excluded from the study. The final sample contained 116 cases (68% of all eligible cases) and 158 controls (74% of those eligible).

Results. Women who reported any perineal use of dusting powders had an adjusted relative risk of 1.1 (95% CI 0.7–2.1) for developing a borderline ovarian tumor. The adjustment was for age, parity, and use of oral contraceptives. It is interesting to note, however, that the crude relative risk was very close to this adjusted value — 1.07 (95% CI 0.66–1.75). Women who used deodorizing powder with or without baby powder (the only powder reported by women who used a second powder) did show an increased risk of borderline tumor development, i.e., a relative risk of 2.8 (95% CI 1.1–11.7). However, the sample size upon which this result was obtained was very small. No other comparisons were statistically significant.

Conclusions. The elevated risk of borderline ovarian cancer among women who specifically used deodorizing powders could have been due to chance or applicable only to borderline but not malignant ovarian tumors. Although Harlow and Weiss believe that this difference between tumor types is unlikely, more study in this area is certainly warranted. Furthermore, because borderline disease is the focus of this paper, one should be concerned with possible misdiagnosis of disease. If even 5% of women diagnosed with the disease are misdiagnosed, the crude relative risk falls to 0.92 (95% CI 0.51–1.60). That is, even the observed elevation in risk disappears. Finally, the authors note the lack of association among women who used only baby powder, which is known to contain pure talc.

6. HAR2

Objective. To determine whether the use of talc in genital hygiene increases the risk for epithelial ovarian cancer.

Methods. Between July 1984 and September 1989, 394 women between 18 and 74 years old were identified as having been diagnosed with borderline or malignant epithelial ovarian cancer at ten different participating Boston metropolitan hospitals. Among these 394 cases, the final sample for analysis was restricted to 235 Caucasian women confirmed to have the disease by pathological review. Population controls were used and were matched on age (within two years) and were all Caucasian. Those having a bilateral oophorectomy were not allowed as controls. The final control sample totaled 239 women. The influence of

confounders and effect modifiers was assessed through stratification and subsequent unconditional logistic regression.

Results. Overall, 49% of cases and 39% of controls reported exposure to talc via direct application to the perineum or to undergarment, sanitary napkins, or diaphragms, which yielded a relative risk of 1.5 (95% CI 1.0–2.1). Among women with perineal exposure to talc, the risk was significantly elevated in subgroups of women who applied it directly as body powder, RR = 1.7 (95% CI 1.1–2.7); on a daily basis, RR = 1.8 (95% CI 1.1–3.0); and for more than 10 years, RR = 1.6 (95% CI 1.0–2.7). There was a greater risk for women with more than 10,000 applications while ovulating and with an intact genital tract, RR = 2.8 (95% CI 1.4–5.4). However, this exposure was only found in 14% of women with ovarian cancer.

Conclusions. These data show an association between an increased risk for epithelial ovarian cancer and long-time use of perineal talc. While this study investigated thoroughly the issue of an association with lifetime use of perineal talc and increased risk of epithelial ovarian cancer and demonstrated a small increased risk of the disease, the cause and effect issue remains uncertain for several reasons. One major difficulty is subject recall. Both cases and controls were unable to trace their use of talc to infancy. Thus, total exposure may be higher than reported in both cases and controls. An important potential confounder that was not accounted for in this study was oral contraceptive use. More controls used oral contraceptives than cases and oral contraceptive use was associated with less reported talc exposure. Thus, use of oral contraceptives is a possible strong confounder that, if properly considered, could eliminate any observed effect. Many separate subgroup analyses were performed in an attempt to ascertain whether any perineal talc exposure was associated with an increased risk of ovarian cancer by the subgroup characteristic. For example, women with no more than a high school education showed an elevated relative risk of 1.7 (95% CI 1.1–3.1), but not women with more than a high school education, RR = 1.4 (95% CI 0.9–2.4). Perhaps the most interesting subgroup analysis indicated that women who used talc prior to 1960 were at an increased risk compared to women who reported use exclusively after 1960. This may be because either the latter group of women has had a shorter latency period or because asbestos, a suspected carcinogen, was removed from talcum powders after 1975. In either case, the large number of subgroup analyses, while interesting and important for suggesting future studies, does not produce unequivocal findings.

7. ROSE

Objective. To study the relationship between fiber exposure and the development of epithelial ovarian cancer.

Methods. Cases and controls were ascertained from the Johns Hopkins Hospital between 1981 and 1985. Originally, 140 newly diagnosed cases who met the eligibility criteria were obtained; of these cases, 77 (55%) were included in the study. Controls were inpatient females who were free of gynecological and malignant conditions. Controls were matched to

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cases by age (within five years), race, and date of diagnostic admission (within one year). Finding controls who met all the matching criteria was a difficult task and controls could not be found for each case. Finally, there were 46 matched sets (46 controls), 31 of whom consisted of two cases and one control. Since no matched control was found for 13 cases, they were excluded from the analysis. It should be noted that 91% of cases and 89% of controls were Caucasian.

Results. An increased risk of ovarian cancer was observed for women who used talc on their sanitary napkins. The observed relative risk was 4.79 (95% CI 1.29–17.79). However, among the remaining nine relative risks computed, no other was statistically significant. Importantly, the relative risk was 1.0 (95% CI 0.2–4.0) for women reporting any genital fiber use versus those women who were not so exposed. This relative risk was adjusted for the number of live births. The crude relative risk for this overall exposure characteristic was 0.84 (95% CI 0.27–2.63).

Conclusions. While there seems to be an elevated risk of ovarian cancer in women who used talc on their sanitary napkins, this relationship does not seem to carry over to the other studies (for example, Harlow [1992] does not show an elevated risk in this category). Furthermore, in questioning women as to whether they used powder on their sanitary napkins, the response was either yes or no. Thus, no measure of length of use was used in this comparison. As stated by the authors, further research is needed to either confirm or refute their findings.

8. HANK

Objective. To assess whether tubal ligation and hysterectomy affect subsequent risk of ovarian cancer.

Methods. This cohort study included women who participated in the Nurses' Health Study from 1976 to 1988. After excluding individuals with a history of cancer (except nonmelanoma skin cancer), with one or both ovaries removed, or who were postmenopausal in 1976, a baseline population of 77,544 women accrued a total of 859,791 person-years of follow-up.

Results. While talc use as a risk factor for ovarian cancer was not the primary focus of this study, indirect information indicated that there was no increased risk of ovarian cancer due to talc use.

Conclusions. This study could be used only indirectly to obtain a relative risk comparing ovarian cancer in talc users versus nonusers. Briefly, the method is as follows: First, the risk period (and thus the person-years and number of cases) is halved for the total study population. Then, subtracting the number of cases and person-years for non-talc users from these halved values, the person-years and number of cases are estimated for talc users. The resulting estimate is a relative risk of 0.62 (95% CI 0.38–1.02).

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9. CHEN

Objective. To study whether there is an increased risk of ovarian cancer in relation to a number of reproductive, demographic, and lifestyle variables.

Methods. A Beijing, China, case-control study matched by age 112 pathologically confirmed epithelial ovarian cancer cases to 224 community controls. Risk of ovarian cancer was evaluated in relation to number of full-term pregnancies, number of ovulatory years, mumps virus infection, and exposure in the perineal region to talc-containing products. Conditional logistic regression was used to control for potential effects of confounding from selected variables.

Results. This study, despite some methodological shortcomings, including not being able to ascertain a complete series of ovarian cancer patients, a high rate of loss due to deaths among cases (67 in all), and exclusion of controls with current health problems, shows results not dissimilar to studies elsewhere in the world. In particular, reproductive and demographic similarities were noted. For example, as parity increased, the risk of ovarian cancer appeared to decrease. Use of dusting powder indicated an increased risk of ovarian cancer. However, the relative risk of 3.9 (95% CI 0.9–10.6) was not statistically significant when adjusted for education and parity, and only 12 women in the total sample of 336 used dusting powder.

Conclusions. This study reports an association between the use of dusting powder and an increased risk of ovarian cancer. However, since less than 4% of all women in the study sample reported using dusting powder, and, when adjusted for confounders, the relative risk was not statistically significant, this association should not be considered definitive.

10. TZON

Objective. To study whether there is any association between an increased risk of ovarian cancer and the following factors: analgesics, hair dyes, perineal talc, and tranquilizers.

Methods. A hospital-based case-control study of ovarian cancer was conducted in Athens, Greece, during 1989–1991. Cases included 181 women with histologically confirmed common, malignant, epithelial ovarian tumors. The control group, 200 women in all, were, as the cases, from the greater Athens area and were visitors of patients hospitalized in the same ward and at the same time as the cancer patients. All interviews were conducted by personnel in the two participating hospitals. The relationships were analyzed using logistic regression, controlling for demographic and reproductive variables.

Results. Among the risk factors studied, there was a statistically significant and dose-dependent association between hair dyeing and the risk of ovarian cancer ($p < 0.01$). There was no evidence that perineal application of talc was associated with an increased risk of ovarian cancer; the crude relative risk was 0.90 (95% CI 0.30–2.74). After adjusting for the other principal variables (i.e., analgesics, hair dyes, and tranquilizers) and an assortment of demographic and reproductive variables, the relative risk was 1.05 (95% CI 0.28–3.98).

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Conclusions. This study fails to indict talc as a potential causal agent of ovarian cancer. However, the authors conclude that the results obtained in this study are not inconsistent with the other studies of the association between perineal talc use and the risk of ovarian cancer.

META-ANALYSES

Is it wise to perform a meta-analysis on the available case-control studies? If so, what concerns are there about its interpretation? These issues are addressed in this section. Several articles have dealt with the use of meta-analysis when its application is based on combining results of independent clinical trials as well as independent epidemiological studies. In particular, Huque (1988), Stein (1988) and Fleiss and Gross (1991) express concerns about study-to-study heterogeneity, study-by-exposure interaction when there is evidence of heterogeneity, study biases and confounders, and whether all studies, or merely the published studies, have been considered in the proposed meta-analysis. If, for example, the issue of study bias has not been properly addressed, spurious associations due to small biases may reach statistical significance when the studies are combined, because the sample size, in effect, has increased. As Mantel states, "In any one study, the bias may fail to be great enough to give rise to statistical significance. But with meta-analysis such biases can combine so as to give rise to an overall appearance of statistical significance."¹

Although these perplexing and difficult shortcomings with regard to a meta-analysis of the existing talc exposure and ovarian cancer studies remain, meta-analysis is of some value in addressing whether there is an association, and, if so, how large its order of magnitude may be.

The four meta-analyses performed consider exposure levels as either "exposed" or "unexposed." When considering crude relative risks and both malignant and borderline tumor types, all nine studies were included. Since BOOT and ROSE do not provide adequate adjusted relative risk estimates, they were not used for the meta-analysis of adjusted risks and both tumor types. The analysis of crude risks and malignant tumors used seven of the studies, and the analysis of adjusted risks and malignant tumors could use only five of the studies (see Table 3).

Before performing a meta-analysis, study combinability should be tested using the technique in DerSimonian and Laird (1986). The calculated value of this statistic, Q , is compared to percentage points for the chi-square distribution with $n - 1$ degrees of freedom, where n is the number of studies. Thus, in each of the analyses the studies are considered combinable and require no extraordinary weighting scheme for the meta-analysis. All of the meta-analyses produce relative risks greater than 1.0 with confidence intervals just excluding the null value.

¹Mantel, Nathan (1990). Personal communication, American University.

TABLE 3. Results of the Meta-Analyses

Analysis	Studies used	<i>Q</i> (degrees of freedom)	RR (95% CI)
Crude risk, both tumor types	All	11.884 (8)	1.27 (1.09–1.48)
Adjusted risk, both tumor types	CRAM, HART, WHIT, HAR1, HAR2, CHEN, and TZON	9.043 (6)	1.31 (1.08–1.58)
Crude risk, epithelial tumors	HART, WHIT, BOOT, HAR2, ROSE, CHEN, and TZON	7.19 (6)	1.20 (1.01–1.44)
Adjusted risk, epithelial tumors	HART, WHIT, HAR2, CHEN, and TZON	7.598 (4)	1.29 (1.02–1.63)

DISCUSSION

Existing evidence linking talc exposure to an increased risk of ovarian cancer cannot be viewed as scientifically conclusive based on a review of the available epidemiological studies. Only the two studies from Boston report an association for ever-users, and the relative risks in nearly every exposure category in almost all studies have been at 2.0 or lower. Given these rather low relative risks reported in the studies, along with the existing biases and confounders that have not been adjusted for, a claim for an increased risk should be viewed with some suspicion. However, all of the meta-analyses arrive at relative risks greater than 1.0 with 95% confidence intervals excluding the null.

There is limited evidence supporting a dose- or duration-response relationship. HAR2 provides the best data set in this respect but suffers from two weaknesses: exposure time after tubal ligation or hysterectomy was excluded, as were periods of anovulation (when a woman was taking oral contraceptives or was pregnant). Since anovulation periods are known to reduce the risk of ovarian cancer and since these adjustments leave controls with shorter periods of exposure, for the most part, whether such an adjustment should be made is open to question. Also, it appears the reasons for a woman using perineal talc have not been well delineated in any of the studies. This may lead to a differential bias, in that the reason for talc use rather than the talc use itself, may actually be a risk factor for ovarian cancer. Finally, HAR2 indicates that even if perineal talc were a risk factor for ovarian cancer, the latency period is very long, perhaps 30 years or more. In fact, HAR2 provides data suggesting an increased risk of ovarian cancer in women who had been using talc prior to 1960.

As can be observed from the objectives in each of the ten studies considered in the previous section, other important factors are correlated with the incidence of ovarian cancer. For example, lifestyle variables, including coffee, tobacco, and alcohol consumption, were studied by WHIT, whereas TZON studied the effects of analgesics and hair dye along with talc. Reproductive issues were the focus of BOOT and HANK.

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Since confounding is a potential concern in any epidemiological study and is especially troublesome when small risks (i.e., relative risk of 2.0 and below) are considered, these other factors need to be considered very carefully in the study of ovarian cancer. For example, it is generally accepted that low parity and nonuse of oral contraceptives are risk factors for ovarian cancer. Unfortunately, these risk factors were not adjusted for in a consistent manner across the studies considered herein. As an example of this, HAR2 fails to adjust for oral contraceptive use even though oral contraceptive users were found to be less likely to report talc exposure than women who did not use oral contraceptives. In this vein it should be noted that among the ten studies in this review, talc exposure was the primary focus in only four studies — CRAM, HART, HAR1 and HAR2.

Other studies have also reviewed the association of talc use and ovarian cancer, but not in the direct framework of either a case-control or cohort epidemiological study. Some of the more important articles are cited. Wehner et al. (1986) state, "Our study, using state-of-the-art techniques in the most suitable animal model available, failed to provide any evidence for such translocation of measurable quantities ($> \sim 0.5$ mg, depending on the radionuclide, detector system and counting time) of talc." This refers to the translocation of talc particles from the vagina to the oviducts of these animals. Longo and Young (1979) implicate asbestos as a possible risk factor, noting its ban in the production of commercial talcum powder in 1973. They note further that exposure to talc from other sources such as chalk, textiles, and crayons is widespread. Recently, a series of articles concerning ovarian cancer risk was published by the Collaborative Ovarian Cancer Group. In the lead article, Whittemore et al. (1992) acknowledge the lack of evidence implicating talc and state, "Other issues, such as the relation of ovarian cancer risk to exposures to talc, tobacco, alcohol, and coffee, were not addressed because too few of the studies had comparable data on the relevant variables."

Additionally, other factors that have not been studied in conjunction with talc exposure may be associated with an increased incidence of ovarian cancer. Cramer et al. (1989) provide some evidence that implicates lactose as a dietary risk factor and transferase as a genetic risk factor. The issues of selection bias and differential bias are not addressed explicitly in these studies. Hence, it is possible, perhaps even likely, that women who have ovarian cancer will selectively remember using talc whereas controls may not have such a remembrance. Further, if there is some hormone, the presence of which may put women at a higher risk for ovarian cancer, then it may also cause perspiration in the perineal area thereby requiring the use of talc.

Thus, the body of knowledge found in the medical literature does not unequivocally support the hypothesis that talc use by women puts them at an increased risk of ovarian cancer. However, the results of the meta-analyses do suggest the possibility of an increased risk of ovarian cancer due to perineal talc use. Further research in this area is warranted by these results.

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APPENDIX

For each of the case-control studies, a relative risk is estimated. The natural logarithm of the relative risk in a study, denoted y_s , is defined in the following equation:

$$y_s = \ln[p_{s1}(1 - p_{s2})/p_{s2}(1 - p_{s1})]$$

The standard error of y_s is given by the equation

$$se_s = \sqrt{1/[n_{s1}p_{s1}(1 - p_{s1})] + 1/[n_{s2}p_{s2}(1 - p_{s2})]},$$

and the limits of the 95% confidence interval for the relative risk are given by

$$\exp(y_s \pm 1.96se_s).$$

The factor by which y_s is weighted in the classical fixed effect analysis, w_s , is given by

$$w_s = 1/(se_s)^2.$$

The "combinability" of the S studies, i.e., the hypothesis that the S underlying odds ratios are equal, may be tested by referring the DerSimonian-Laird statistic

$$Q = \sum w_s (y_s - \bar{y})^2 \text{ with } \bar{y} = \sum w_s y_s / \sum w_s$$

to percentage points of the chi-square distribution with $S - 1$ degrees of freedom. The relative risk estimate is now given as

$$\overline{RR} = \exp(\bar{y}),$$

and the limits of the 95% confidence interval for the overall relative risk are given by

$$\exp\left(\bar{y} \pm 1.96/\sqrt{\sum w_s}\right).$$

This interval will not be symmetric about \overline{RR} .

Exhibit 50

Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11, 933 Subjects from Sixteen Observational Studies

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Abstract. *Objective:* Prior epidemiological studies suggest an association between perineal cosmetic talc use and increased risk of epithelial ovarian cancer. A meta-analysis was performed to evaluate this suspected association. *Materials and Methods:* Using previously described methods, a protocol was developed for a meta-analysis examining the association between perineal talc use versus non-use and the development of invasive epithelial ovarian cancer. Literature search techniques, study inclusion criteria and statistical procedures were prospectively defined. Data from observational studies were pooled using a general variance based meta-analytic method employing confidence intervals previously described by Greenland. The outcome of interest was a summary relative risk (RRs) reflecting the risk of ovarian cancer development associated with perineal talc use versus non-use. Sensitivity analyses were performed when necessary to explain any observed statistical heterogeneity. *Results:* Sixteen observational studies meeting protocol specified inclusion criteria were located via a comprehensive literature search. These studies enrolled a total of 11,933 subjects. Analysis for heterogeneity demonstrated that the data were homogenous ($p = 0.17$) and could be combined in a meta-analysis. Pooling all sixteen studies yielded a RRs of 1.33 (CI = 1.16-1.45), a statistically significant result suggesting a 33% increased risk of ovarian cancer with perineal talc use. Despite this finding, the data showed a lack of a clear dose-response relationship making the RRs of questionable validity. Further sensitivity analyses showed that hospital-based studies showed no relationship between talc use and ovarian cancer risk, i.e. RRs 1.19 (0.99-1.41) versus population-based studies (RRs = 1.38, CI = 1.25-

1.52). This suggests that selection bias and/or uncontrolled confounding may result in a spurious positive association between talc use and ovarian cancer risk in population-based studies. *Conclusion:* The available observational data do not support the existence of a causal relationship between perineal talc exposure and an increased risk of epithelial ovarian cancer. Selection bias and uncontrolled confounding may account for the positive associations seen in prior epidemiological studies.

Ovarian cancer represents a major cause of mortality and morbidity among women in the United States with over 25,000 cases diagnosed each year. This tumor represents the fourth most common gynecological cancer in the U.S. with over 15,000 deaths annually (1). Overall, ovarian neoplasms account for over 50% of all deaths from tumors of the female genital tract. Ovarian cancer is more common in industrialized countries implicating environmental factors in its etiology.

In 1982, Cramer *et al.* published the results of a case control study implicating perineal cosmetic talc use in the development of ovarian cancer (2). Subsequently, a number of additional studies have shown small but increased risk among women using cosmetic talcum powder. These statistical associations raise concerns that there may be a cause-effect relationship between perineal talc exposure and ovarian carcinogenesis. This concern is further fuelled by the structural similarity between talc and asbestos, a well-recognized human carcinogen.

Despite the availability of a number of observational studies suggesting an association between perineal talc application and ovarian cancer development, serious questions remain regarding the validity of this finding. These include: (1) the relatively small sample size of most studies limiting statistical power to detect an effect; (2) lack of consistent positive association across studies; (3) absence of demonstrable dose-response relationship; (4) lack of supporting evidence of carcinogenicity from animal or *in vitro* analyses; and (5) the possible presence of uncontrolled confounding producing a spurious positive association

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between talc use and ovarian cancer risk. Due to the above-cited limitations of the available database, a meta-analysis was performed in order to statistically pool all available studies addressing this issue. The results of this analysis should provide a clearer understanding of the association (if any) between perineal talc use and ovarian cancer risk.

Materials and Methods

The methods employed in this analysis have been previously described (3). Briefly, a study protocol was prospectively developed that outlined the purpose and methods of the analysis. Eligibility criteria for the studies were determined prospectively, as were the specific data elements to be extracted from each trial. A plan for data analysis was also formulated as part of the study protocol. A data extraction form was designed for recording relevant data from each published study.

Literature retrieval was performed by previously described methods (8). A MEDLARS search was conducted covering the years January 1966 to January 2001. The CancerLit as well as the EMBASE databases were also fully explored, as was the CD-ROM version of Current Contents. The search included all languages. The search terms used were talc exp ovarian neoplasms. Manual searches of study bibliographies and a review of relevant textbooks supplemented electronic database searches. Bibliographies of relevant review articles were also searched. If a series of papers was published, all data were retrieved from the most recent report.

The initial citations (in the form of abstracts) from this literature search were screened by a physician investigator (oncologist) to exclude those that did not meet protocol specified inclusion criteria. The reasons for rejection included: animal studies, *in vitro* studies, review articles, letters to the editor, abstracts, non-peer reviewed articles and papers dealing with only non-epithelial ovarian tumors. Citations selected from this initial search were subsequently screened for eligibility using the following criteria:

- (1) observational studies enrolling patients with histologically-proven epithelial ovarian tumors excluding tumors of "borderline malignant potential",
- (2) studies enrolling adult patients only (*i.e.* 18 years of age or older),
- (3) availability of data documenting type of talc exposure (*e.g.* dusting perineum *versus* sanitary napkins *etc.*) and
- (4) odds ratio or relative risk with 95% confidence interval for each study or availability of raw data to calculate these parameters.

Citations meeting the above criteria were entered onto an accept log and copies of full papers were obtained. The key data elements extracted from each trial included: number of cases and controls, frequency of perineal talc use, origin of study subjects (*i.e.* hospital *versus* population-based), factors (if any) used to statistically adjust study odds ratios or relative risks, case /control response rates and percentage of subjects reporting talc use. Two researchers performed the data extraction. Differences in data extraction forms were resolved by consensus.

Statistical methods. The data analysis was performed according to meta-analysis procedures previously described by Greenland (4). This meta-analysis method is a general variance-based method employing confidence intervals. Because the variance estimates are based on adjusted measures of effect and on the 95% confidence interval for the adjusted measure, the confidence interval methods do not ignore confounding and are the preferred methodology for observational data. The estimate of the 95% confidence interval from each study is used to estimate the variance of each study's effect measure, *i.e.*

$$\ln RR_s = \frac{\sum (w_i \times \ln RR_i)}{\sum w_i}$$

where

$$w_i = \frac{1}{\text{variance } RR_i}$$

The RR_i are estimates of relative risk and in this instance have been measured as odds ratios. Estimating the variance from the 95% confidence interval is given by,

$$\text{variance } RR_i = \left[\frac{\ln (RR_i + RR_i)}{1.96} \right]^2$$

where RR_i is the estimate of the relative risk in the i th study and RR_i is the lower bound of the 95% confidence interval for the study.

A 95% confidence limit for the estimated relative risk is determined as,

$$95\% \text{ CI} = e^{\ln RR_s} \pm 1.96 \times \sqrt{\text{variance}_x}$$

and

$$\text{variance}_x = \frac{1}{\text{sum weight}_i}$$

Prior to estimation of a summary relative risk, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the studies (3). If Q exceeds the upper tail critical value of Chi-square ($p < 0.10$) at $k-1$ *df* (where k equals the number of studies analyzed or the number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies are not measuring an effect of the same size. In this instance, calculation of a pooled estimate of effect (*i.e.* RR_s) may be of questionable validity. Study effect sizes may be disaggregated by grouping studies into appropriate categories until Q is not rejected within those categories or regression techniques can be employed. That is, reasons for the observed heterogeneity must be sought. In essence, Q is a diagnostic tool for determining if all the variance in the observed effect sizes is accounted for.

Using the general variance-based meta-analysis method employing confidence intervals proposed by Greenland, Q is calculated as:

$$Q = \sum [\text{weight}_i \times (\ln OR_s - \ln OR_i)^2]$$

Where OR_s and i are estimated as described above.

Results

The literature search yielded seventeen studies that appeared to meet protocol specifications and full papers were obtained for review (2,5-20). Further review showed that the paper by Hankinson *et al.* (12) used the same data as a subsequent paper by Gertig *et al.* (10) from the same laboratory. Therefore, only reference 12 was included in the meta-analysis. The remaining sixteen papers met protocol specified inclusion criteria.

Table I provides an overview of the included reports. A total of 11,933 subjects were enrolled in fifteen case-control studies and one cohort study. Five of the sixteen reports were hospital-based with the remainder being population-based analyses. The individual odds ratios listed in Table I reflect the odds of exposure in cases and controls with an odds ratio of greater than one suggesting a positive association, *i.e.* an

Table 1. Overview of included studies.

Author	#cases	#controls	Freq. powder use	OR (95% CI)	Adjustments to OR	Hospital vs population
Booth (5)	235	451	never vs ever	1.29 (0.92-1.80)	-age, SES	H
Chang (6)	450	564	none vs any	1.42 (1.08-1.86)	-age, yrs OC use, #full term pregnancies, duration of breast feeding/pregnancy, tubal ligation, hysterectomy, mother or sister with ovarian/breast cancer	P
Chen (7)	112	224	never vs ever	3.9 (0.9-10.6)	-education, parity	P
Cook (8)	313	422	none vs any	1.5 (1.1-2.0)	-age, education, income, marital status, BMI, OC use, parity	P
Cramer (9)	563	523	never vs any	1.60 (1.18-2.15)	-age, study center, tubal ligation, BMI, parity, OC use, primary relative with breast or ovarian cancer	P
Cramer (2)	215	215	none vs any	1.92 (1.27-2.89)	-parity, menopausal status	P
Gertig (10)	307		never vs ever	1.05 (0.84-1.32)	-age, parity, duration of OC use, BMI, tubal ligation, smoking, post menopausal hormone use	P
Godard (11)	170	170	never vs ever	2.49 (0.94-6.58)	-age, OC use, parity, tubal ligation hysterectomy, alcohol use	P
Harlow (13)	235	239	never vs any	1.5 (1.0-2.1)	-parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	p
Harlow (14)	116	158	none vs any	1.1 (0.7-2.1)	-age, parity, OC use	P
Ness (15)	767	1,367	never vs ever	1.5 (1.1-2.0)	-age, parity, family Hx ovarian cancer, race, OC use, tubal ligation, hysterectomy, breast feeding	P
Purdie (16)	824	860	never vs ever	1.27 (1.04-1.54)	-parity, hysterectomy, tubal ligation, OC use, age, education, BMI, smoking, family Hx cancer	P
Rosenblatt (17)	77	46	never vs any	1.0 (0.2-4.0)	-live births	H
Tzonou (18)	189	200	never vs any	1.05 (0.28-3.98)	-age, education, weight, age at menarche, menopause, menopausal status, parity, age at first birth, tobacco use, coffee/ETOH use, hair dying	H
Whittemore (19)	188	539	never vs ever	1.45 (0.81-2.60)	-parity, OC use	H
Wong (20)	499	755	never vs ever	1.0 (0.8-1.3)	-OC use, smoking, parity, family Hx ovarian CA, age at menarche, menopausal status, income, education, geographic location, tubal ligation/hysterectomy	H

OR, odds ratio; CI, 95% confidence interval; OC, oral contraceptive; Hx, history.

increased risk of ovarian cancer. Individual study odds ratios (OR) ranged from 1.0 to 3.9. Nine of the sixteen reports provided some information on dose-response (2, 5, 6, 8, 10, 13, 15, 19, 20). This took the form of either stratifying study subjects on number of perineal talc applications per month or number of years used. As seen in the table, all studies adjusted study odds ratios by various factors although there

were differences in the specific adjustments across studies.

Prior to combining all studies to derive a summary estimate of effect (*i.e.* a summary relative risk, RRs) a statistical test for homogeneity was performed, Q). This gave a value of Q equal to 20.29. With 15 degrees of freedom, the *p* value associated with a Q of this size is 0.17. This indicates that the studies are homogeneous (*i.e.* the studies are measuring

effects of similar magnitudes). Given the lack of statistical heterogeneity, the data were pooled for calculation of a summary relative risk.

Pooling data from all sixteen studies yielded a summary relative risk of 1.33 with a 95% confidence interval of 1.16-1.45, a statistically significant result suggesting a 33% increased risk of developing ovarian cancer with perineal talc exposure *versus* no exposure. Despite the finding of a positive association, demonstration of a dose-response relationship is an important criterion for making causal inferences from epidemiological data. If no relationship exists, a causal link between exposure and disease is questionable. The summary relative risk may in fact be spurious due to bias or uncontrolled confounding.

Seven studies included dose-response data stratified by number of talc application to the perineum per month (Table II). A comparison was made across these studies comparing the lowest recorded exposure category with the highest exposure level. This showed a RRs of 1.83 (1.55-2.15) for the lowest talc exposure group, *i.e.* an 83% increase in ovarian cancer risk *versus* a RRs of 1.21 (1.00-1.45) for the highest talc exposure category (the latter being a non-statistically significant result). These data suggest an inverse relationship between talc exposure and ovarian cancer risk. Unfortunately, only limited data were available in that (1) only a small minority of studies contained dose-response information of any type and (2) substantial differences existed in dose stratification levels among the studies reporting such information. It was therefore not possible to perform more sophisticated modeling of dose-response data (21). Nonetheless, the apparent lack of a dose-response relationship requires further exploration in additional studies. It must be considered that the carcinogenic activity of talc may resemble that of asbestos, although this remains purely speculative. The relationship between asbestos exposure and mesothelioma risk lack a clear dose-response relationship (22). Elucidation of this relationship is complicated by possible differences in biological activity based on fiber type and, possibly more importantly, fiber dimensions. Time since exposure may be a more important parameter in asbestos-related mesothelioma risk than total exposure, although this remains uncertain. How these features of asbestos-related mesothelioma compare to the possible biological activity of cosmetic talc remains questionable.

On further examining Table II, the lowest talc exposure category in the Cramer *et al.* study is "less than 30" applications per month (9). This value is not consistent with the other "low exposure" categories, *i.e.* it is a substantially greater value than seen in any other study. Exposure categories must be roughly similar in order to make valid comparisons across studies. If a sensitivity analysis is performed by dropping this study from the pooled result, a summary relative risk of 1.43 (1.14-1.85) results. Taken together, these data show a lack of a clear dose-response relationship.

Table II. Dose response data.

Reference	Years of talc use/OR + 95% CI		#talc application/month /OR + 95% CI	
5	NG		1x	0.7 (0.3-1.8)
			4x	2.0 (1.3-3.4)
			30x	1.3 (0.8-1.9)
6	<30	1.7 (1.09-2.68)	<10	1.84 (1.24-2.73)
	30-40	1.44 (0.96-2.15)	10-25	1.13 (0.74-1.72)
	>40	0.96 (0.54-1.38)	>25	0.95 (0.61-1.49)
8	0-5.5	1.8 (0.9-3.5)	NG	
	5.5-13.5	1.6 (0.9-2.9)	NG	
	13.5-27	1.2 (0.6-3.4)	NG	
	>27	1.8 (0.9-3.4)	NG	
9	<20	1.9 (1.2-3.0)	<30	2.2 (1.4-3.6)
	20-30	1.3 (0.8-2.3)	30-39	1.2 (0.8-1.8)
	>30	1.4 (0.9-2.3)	40+	1.6 (0.8-3.1)
10	NG		4-24	0.99 (0.67-1.46)
			>=30	1.12 (0.82-1.55)
13	<10	1.2 (0.5-2.6)	<5	1.5 (0.8-2.7)
	10-29	1.6 (1.0-2.7)	5-29	1.2 (0.6-2.2)
	>=30	1.6 (1.0-2.7)	>=30	1.8 (1.1-3.0)
15	,1	2.0 (1.0-4.0)	NG	
	1-4	1.6 (1.1-2.3)		
	5-9	1.2 (0.8-1.9)		
	10+	1.2 (1.0-1.5)		
19	1-9	1.60 (1.00-2.57)	1-20	1.27 (0.82-1.96)
	10+	1.11 (0.74-1.65)	>20	1.45 (0.94-2.22)
20	1-9	0.9 (0.6-1.5)	NG	
	10-19	1.4 (0.9-2.2)		
	>=20	0.9 (0.6-1.2)		

NG, not given.

Fifteen of the included studies were of case-control design while reference 10 was a cohort study. Since study design may effect study outcome, a sensitivity analysis was performed by excluding Gertig *et al.* from the analysis and recalculating RRs. This gave a summary relative risk of 1.36, a result almost identical to the initially calculated RRs. Therefore, study design showed little effect on the pooled estimate to effect.

Table I lists the adjusted odds ratios for each included report and the specific adjustments made. As noted earlier, a number of factors are known to influence ovarian cancer risk either positively or negatively, such as parity, oral contraceptive use and infertility. That is, few data are available detailing the demographic and hygienic practices of women using cosmetic talc. Since there are some existing data suggesting a positive association between a high fat diet and increased ovarian cancer risk, a relationship may exist

between weight/body mass index and talc use (10). A sensitivity analysis was performed pooling the six studies that controlled for these parameters (8-10, 13, 16, 18). The summary relative risk obtained was 1.32 with a 95% confidence interval of 1.16-1.49. This analysis showed minimal change in the RRs suggesting that the body mass index / weight does not significantly impact the observed association between talc use and ovarian cancer risk.

Table I shows that five of the included case-control studies were hospital-based (5, 17-20) while the remaining studies were population-based. This fact is important since referral patterns may impact study results. If referral patterns among hospitals in a given city or region differ, the over-referral of exposed cases to one hospital implies an under-referral of cases to the others. Due to "differential referral", a factor may be associated with increased disease risk in one hospital-based study and protective in another. In an individual study, pooling data across hospitals helps eliminate bias from differential admission of cases. Pooling data from several sources in a meta-analysis, as done in the present report, partially accomplishes this. Stratifying the meta-analysis on the source of patients, *i.e.* hospital-*versus* population-derived, demonstrated that the summary relative risk for population-based studies was 1.38 (1.25-1.52) suggesting a 38% increased risk of ovarian cancer among talc users *versus* non-users. Interestingly, pooling all hospital-based studies yielded a RRs of 1.19 (0.99-1.41), a non-statistically significant result indicating a lack of association between talc use and ovarian cancer risk. More frequent talc use among hospital-based control patients *versus* population-derived controls does not explain this finding since the proportion of controls using talc was the same in both groups, *i.e.* 32%. Other factors account for this difference in outcome.

As seen in Table I, the individual study odds ratios are generally in the range of 1.0-2.0. Odds ratios of this magnitude are considered "weak effects". This fact is important in that misclassification of only a small proportion of cases could move an odds ratio from non-statistically significant (*i.e.* OR = 1.0) to significant (*e.g.* 1.2-1.5 *etc.*). One possible explanation of the potentially spurious positive association between talc use and ovarian cancer risk is the existence of a "treatment effect" among cases. Particularly among population-based studies, a varying proportion of cases will be prevalent rather than incident. Some patients with ovarian cancer will undergo treatment with radiation, chemotherapy and/or surgery. Side-effects from treatment may prompt talc use among some patients. Although many questionnaires may specify talc use prior to diagnosis, patients may not always make the distinction between pre-diagnosis and post-treatment use. Exposure misclassification among "prevalent" cases may cause a spurious finding of an association when none, in fact, exists. No information is available from the published studies regarding types of treatment administered to study subjects. This precluded further exploration of the

above hypothesis. If data on time from diagnosis to interview was known, patients could be stratified on this parameter with re-calculation of a summary relative risk. Unfortunately, none of the included studies provided such information.

Overall, the above findings of selection bias due to study design and the clear lack of a dose-response relationship between talc use and ovarian cancer risk brings the previously suggested association into question. The data presented in this meta-analysis do not support a cause-effect relationship between perineal cosmetic talc use and the risk of ovarian cancer development.

Discussion

Talc is a hydrous magnesium silicate with a structural similarity to asbestos fibers. Asbestos is a family of mineral fibers with well-recognized carcinogenic properties. Inhalation of asbestos is associated with an increased risk of lung cancer and mesothelioma, a highly lethal tumor of the chest or abdomen. Mesothelioma may also affect the testis as well as the pericardium. Interestingly, asbestos and talc are often found together in nature with talc deposits contaminated with asbestos fibers (21).

A study of 21 consumer talcum powders labeled as baby powders, facial powders or body powders, obtained from retail stores in New York City between 1971 and 1975 reported that ten contained concentrations of tremolite and anthophyllite asbestos ranging from 0.2 to 14.0 percent (22). Voluntary guidelines were established by the cosmetic industry in 1976 to limit the content of asbestiform fibers in commercial talc preparations, although the magnitude of the risk of ovarian cancer as a result of perineal exposure to talc remains unclear.

In the 1960's it was recognized that female asbestos workers demonstrated an increased risk of ovarian cancer and other intra-abdominal tumors (23). Subsequent retrospective cohort studies of women in various asbestos industries showed a two-fold increase in ovarian cancer with a suggested dose-response relationship. Heller *et al.* (24) showed that substantial amounts of asbestos fibers can be found in ovarian tissue derived from women with fathers or husbands employed in asbestos-related occupations. Women with domestic asbestos exposure were twice as likely to have asbestos fibers in the ovarian tissue as compared with those without such an exposure history. Nonetheless, migration of talc particles from the lower female genital tract to the ovary has not been demonstrated conclusively in other studies (25-27). Asbestos contamination of talc has been identified in the past but current production methods limit or completely eliminate contamination. Asbestos contamination of talc complicates studies that examine ovarian cancer risk among talc workers since it is not possible to determine with certainty the possible independent contribution of talc to cancer risk.

Cramer *et al.* conducted the first study suggesting a link

between cosmetic talcum powder use and ovarian cancer (2). Since that time, a number of additional reports have addressed this question with most showing odds ratios ranging between 1.0 and 2.0. Odds ratios of this magnitude, *i.e.* weak associations, are difficult to interpret. This dogma is based on the fact that the investigator cannot directly manipulate the levels of the exposure of interest or extraneous factors that could affect study findings. Attempts to control for external factors are accomplished by statistical manipulations of collected data. However, this process depends on the accuracy and completeness of data collection. Further, the correct choice and interpretation of both statistical models and statistical findings can also be contentious. For these reasons, odds ratios below 1.5 or 2.0 are often dismissed by epidemiologists as uninterpretable. The danger of this, however, is that an association may be weak but real.

Meta-analysis has been employed in an attempt to overcome the problem of weak associations. If meta-analyses show that the patterns of low relative risk or odds ratios are elevated across all relevant studies in different populations, these weak associations are less likely to be due to study bias or uncontrolled confounding. Nonetheless, even in this instance, if a bias affects all studies in the same manner, an association may be shown although the finding is spurious. If a statistical test for heterogeneity shows effects of different magnitudes across studies, sensitivity analyses can be employed to determine the source of observed variability and thereby identify biases due to study design, case / control selection *etc.* This systematic evaluation of heterogeneity provides valuable information that can contribute to a clearer understanding of possible causal associations and improvement in the design of more definitive studies.

The meta-analysis presented above shows inconsistencies in the available data, *i.e.* clear differences in study findings related to whether studies were hospital-based or population-based. The differences in findings from various research groups may not be entirely due to differences in the source of study subjects *per se* (selection bias), but may be due to the differences in the proportion of incident *versus* prevalent cases across studies. As explained earlier, a "treatment effect" operative among prevalent cases could account for the spurious positive association seen in some studies. Unfortunately, it is not possible to prove this definitively given the existing data-base. Also, the behavioral aspects of talc use are poorly defined. That is, very limited data exist regarding the demographics of hygienic talc use. This information might be useful in providing additional insight into how talc use differs across segments of the female population and how it relates to ovarian cancer risk, if at all.

In addition, the present meta-analysis shows a lack of a clear dose-response relationship between talc exposure and cancer risk. As discussed by Evans (28), demonstration of a dose-response relationship is an important criteria for drawing causal inferences in chronic disease epidemiology. Inability to show increasing incidence with increasing exposure makes a causal association less likely. In fact, the available data seem to indicate an inverse dose-response relationship which is counter-intuitive.

In summary, pooling data from the sixteen available observational studies examining the relationship between perineal use of cosmetic talc and the development of invasive

epithelial ovarian cancer failed to show evidence of a causal relationship. Future studies need to examine whether misclassification based on post-treatment talc use leads to a false-positive association between talc use and increased ovarian cancer risk. Additional information on the "demographic profile" of talc users may also provide the basis for improved study design.

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Exhibit 51

Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies

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Prior work suggests an association between perineal use of cosmetic talc and increased ovarian cancer risk. A meta-analysis was performed to examine this hypothesis by evaluating ovarian cancer risk associated with direct exposure of the female genital tract to talc via dusting of contraceptive diaphragms. Data were pooled from epidemiological studies using a general variance-based meta-analytic method that employs confidence intervals. The outcome of interest was a summary relative risk reflecting the risk of ovarian cancer development associated with the use of cosmetic talc on contraceptive diaphragms. Sensitivity analyses were performed to explain any observed statistical heterogeneity and to explore the influence of specific study characteristics on the summary estimate of effect. Initially, combining homogeneous data from nine case-control studies yielded a non-statistically significant summary relative risk of 1.03 (0.80–1.37), suggesting no association between talc-dusted diaphragms and ovarian cancer development. Sensitivity analyses were performed to evaluate the robustness of this finding. All resultant summary relative

risks were not statistically significant. The available epidemiological data do not support a causal association between the use of cosmetic talc-dusted diaphragms and ovarian cancer development. *European Journal of Cancer Prevention* 16:422–429 © 2007 Lippincott Williams & Wilkins.

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Introduction

Ovarian cancer represents a major cause of cancer-related morbidity and mortality in the United States with an estimated 22 000 new cases diagnosed in 2005 (Boger-Meigiddo and Weiss, 2005). It is the seventh most common cancer in women and ranks fourth as a cause of cancer deaths among female individuals from the United States, with some 16 000 succumbing to the disease this year. The lethality of ovarian tumors is in large part due to the fact that clinical symptoms tend to occur late in the natural history of the disease and the lack of screening tests allowing for early diagnosis. In fact, approximately 60% of patients are diagnosed with late-stage disease (stage III and IV) vastly diminishing the chance of long-term survival (approximately 10% at 5 years from diagnosis) (Richardson *et al.*, 1985).

Primary prevention of ovarian cancer remains elusive as a clear etiology for the vast majority of cases is unknown. Nonetheless, prior epidemiological research suggests a number of risk factors, including age (older versus younger), nulliparity, first pregnancy after the age of 35 years, diet high in saturated fats, positive family history of

ovarian/breast cancer and race (white versus African American) (Baker and Piver, 1994; Tortolero-Luna and Mitchell, 1995; Daly and Orams, 1998). Clear geographic differences in incidence exist. The highest rates are found in industrialized countries versus underdeveloped nations (Ioka *et al.*, 2003), implicating environmental factors in ovarian cancer etiology. The one exception is highly industrialized Japan (Ioka *et al.*, 2003) with a low annual incidence of approximately 3/100 000. Interestingly, Japanese woman who migrate to the United States experience an increased occurrence of this disease, further suggesting environmental factors in its cause.

In 1982, Cramer *et al.* (1982) published the first study suggesting a link between use of cosmetic talc and the risk of developing ovarian cancer. Subsequently, a number of additional reports have shown a small but increased risk among women using cosmetic talc products, although this finding is not universal (Chang and Risch, 1997). These statistical associations raise concerns that a cause-effect relationship may exist between talc exposure (particularly perineal use) and ovarian carcinogenesis.

Further fueling concerns about this association is the mistaken, but often repeated, assertion that asbestos and talc are biologically similar; that is, they may exhibit similar disease-causing potential (Wong *et al.*, 1999). While talc and asbestos are both silicates, they bear little resemblance structurally or in their biological properties. Asbestos fibers are well recognized human and animal carcinogens with substantial supporting epidemiological and in-vivo evidence available in the published literature (Huncharek, 1986; Mossman and Gee, 1989). Asbestos is known to induce peritoneal (and pleural) mesotheliomas among occupationally and environmentally exposed cohorts and some evidence exists suggesting that asbestos can also cause ovarian neoplasms in humans (Acheson *et al.*, 1982).

Although in the experimental setting translocation of talc particles to the human ovary can occur with deliberate or inadvertent manipulations of patients in the supine position (Wehner, 1998), it is unknown whether cosmetic use of talc in the perineal area can routinely penetrate the female reproductive tract and reach the ovary against physiological forces working in the opposite direction. The existing epidemiological literature focuses primarily on external perineal exposure. It appears, however, that the talc-ovarian cancer hypothesis could be tested with better precision and validity if the exposure to the suspected carcinogen was directly to the reproductive tract. A common route for such an exposure is via talc dusting of contraceptive diaphragms, a well documented practice in the relevant epidemiological literature. Intuitively, the possible association of ovarian cancer with talc-dusted diaphragms appears to provide a more rational test of this cause-effect hypothesis. Therefore, the present report describes the results of a meta-analysis pooling data from nine epidemiological studies examining the risk of ovarian cancer associated with the use of cosmetic talc on diaphragms.

Methods

The methods employed in the design and execution of this analysis have been previously described (Greenland, 1986; Cooper and Hedges, 1994). A study protocol was prospectively developed outlining the purpose and methods; that is, a meta-analysis examining the risk of developing ovarian cancer associated with use of talc-dusted contraceptive diaphragms. Eligibility criteria for study inclusion were determined prospectively as were the specific data elements to be extracted from each published report. The study protocol included details of the planned statistical analysis.

We used a data extraction form designed for recording relevant information from each selected report. Two researchers performed data extraction with differences in extraction forms resolved by consensus. Other data

collected but not included in the eligibility criteria were the number of patients in each study, study odds ratios or relative risks, 95% confidence intervals and type of statistical adjustments made, if any, by individual study authors.

Literature search

Information retrieval was performed by previously described methods (Cooper and Hedges, 1994). We conducted a MEDLARS search of the literature published between January 1966 and March 2005, as well as a review of Cancer Lit and the CD-ROM version of Current Contents. The search criteria included all languages. The search terms used were talc exposure and ovarian neoplasms. If a series of articles was published, all data were retrieved from the most recent article. The literature search also included hand searches of bibliographies of published reports, review articles and textbooks.

The initial citations (in the form of abstracts) from this literature search were screened by a physician investigator to exclude those that did not meet inclusion criteria. Reasons for rejection included study designs other than case-control, cohort or randomized controlled trials; animal or in-vivo studies; abstracts; review articles and non-peer reviewed articles. Eligibility criteria included, observational studies or clinical trials enrolling patients with histologically proven ovarian tumors of all histologies, studies enrolling only adult patients (i.e. 18 years or older), availability of data documenting type of talc exposure, in this instance, dusting of diaphragms, and availability of odds ratios or relative risks with 95% confidence intervals for each report or availability of raw data to calculate these parameters.

Statistical analysis

We performed data analysis according to meta-analytic procedures described by Greenland (1986). This method of meta-analysis is a general variance-based method employing confidence intervals. As the variance estimates are based on the adjusted measures of effect, the confidence interval methods do not ignore confounding and are the preferred methodology for pooling observational studies.

For each included study, we derived odds ratios reflecting the risk of developing ovarian cancer associated with the practice of dusting contraceptive diaphragms with cosmetic talc and determined the natural logarithm of the estimated relative risk for each data set followed by calculation of an estimate of the variance. We used the estimate of the 95% confidence interval from each study to calculate the variance of each study's measure of effect.

We calculated a weight for each included analysis as $1/\text{variance}$ followed by a summation of the weights. We then determined the product of the study weight and the natural logarithm of the estimated relative risk and performed a summation of these products. Finally, a summary relative risk and 95% confidence interval were determined.

Before the estimation of a summary relative risk, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the included studies (Greenland, 1986). If Q exceeds the upper tail critical value of χ^2 ($P < 0.10$) at $k-1$ d.f. (where k equals the number of studies analyzed or the number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies do not measure an effect of the same size. In this instance, calculation of a pooled estimate of effect (i.e. relative risks) may be of questionable validity. Possible explanations for the observed heterogeneity must be sought to provide the most rational interpretation of the summary relative risk. Sensitivity analyses and or further stratified analyses are then performed based on the magnitude of Q .

Results

The literature search yielded 17 studies that appeared to meet protocol specifications and full papers were obtained for review (Hartge *et al.*, 1983; Richardson

et al., 1985; Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow and Weiss, 1989; Chen *et al.*, 1992; Harlow *et al.*, 1992; Rosenblatt *et al.*, 1992; Tzonou *et al.*, 1993; Purdie *et al.*, 1995; Cook *et al.*, 1997; Goddard *et al.*, 1998; Cramer *et al.*, 1999; Gertig *et al.*, 2000; Ness *et al.*, 2000). Upon further review, nine of these met the specified inclusion criteria. Table 1 provides an overview of the nine reports included in the meta-analysis (Hartge *et al.*, 1983; Richardson *et al.*, 1985; Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow and Weiss, 1989; Harlow *et al.*, 1992; Rosenblatt *et al.*, 1992; Cook *et al.*, 1997; Ness *et al.*, 2000). A total of 2281 ovarian cancer cases and 3608 controls were enrolled in nine case-control studies. Table 1 also specifies which reports were hospital based versus those that were population based. Only Cook *et al.* (1997) and Harlow and Weiss (1989) used both population-derived cases and controls. All of the other studies listed as 'population based' used hospital-derived cases. The individual study odds ratios listed in Table 1 reflect the odds of exposure in cases versus controls, with an odds ratio greater than one suggesting a positive association, that is, an increased risk of ovarian cancer among women using talc-dusted diaphragms.

Before combining all studies to derive a summary estimate of effect (i.e. a summary relative risk) a statistical test for heterogeneity was performed (Q). This gave a value of Q equal to 10.75. With eight degrees of freedom, the P value associated with a Q of this size is 0.22. This indicates that the studies are homogeneous; that is, the studies are measuring an effect of similar

Table 1 Overview of included studies

Study (year)	Number of cases/controls	Percentage eligible cases included	Adjusted OR	95% CI	Adjustments to OR	Epithelial tumors only	Borderline tumors incl.	Stratification by histology	H/P
Booth <i>et al.</i> (1989)	235/451	84	0.75	0.85–2.02	Age, SES	Y	Y	N	H
Cook <i>et al.</i> (1997)	313/422	64	0.80	0.40–1.40	Age	Y	N+	Y	P
Cramer <i>et al.</i> (1982)	215/215	72	1.56	0.62–3.88	Parity, menstrual status	Y	Y	Y	P
Harlow <i>et al.</i> (1992)	235/239	59	1.20	0.60–2.40	Parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	Y	Y	Y	P
Harlow and Weiss, 1989	116/158	68	0.50	0.20–1.30	Age, parity, use of oral contraceptives	N/A	All	N/A	P
Hartge <i>et al.</i> (1983)	135/171	69	0.80	0.40–1.40	Age, race, hospital	Y	Unknown	N	H
Ness <i>et al.</i> (2000)	767/1367	61	0.60	0.30–1.20	Age, gravity, race family HX ovarian cancer, oral contraceptive use, tubal ligation, hysterectomy, breast feeding	Y	Y	N	P
Rosenblatt <i>et al.</i> (1992)	77/46	55	3.0	0.80–10.8	Obesity, SES, religion, number of live births, OC use	Y	Unknown	N	H
Whittemore <i>et al.</i> (1988)	188/539	NG	1.5	0.63–3.58	Parity, use of oral contraceptives	Y	Unknown	N	H

SES, socio-economic status; OR, odds ratio; CI, confidence interval; H/P, hospital based/population based; N+, separate analyses done for borderline versus invasive tumors.

magnitudes. Given the lack of statistical heterogeneity, the data were pooled for calculation of a summary relative risk.

Table 1 shows that adjusted odds ratios ranged from 0.60 (Booth *et al.*, 1989) to 3.0 (Rosenblatt *et al.*, 1992), with adjustment parameters specified along with 95% confidence intervals. Of note, none of the reports showed a statistically significant odds ratio. Initial pooling of data from all nine reports yielded a summary relative risk of 1.03 with a 95% confidence interval of 0.80–1.33, a non-statistically significant result suggesting no association between talc/diaphragm use and ovarian cancer risk (see Fig. 1).

Upon closer scrutiny of the available data, further sensitivity analyses were performed as described below. The data provided by Booth *et al.* (1989) did not explicitly provide data on talc use via contraceptive diaphragms and such use could only be assumed. As the data were questionable in this respect they were dropped from the analysis and a summary relative risk was recalculated. The resultant relative risk was 1.12 with a 95% confidence interval of 0.84–1.48. Therefore, the results remained statistically non-significant despite removal of these data from the summary estimate of effect.

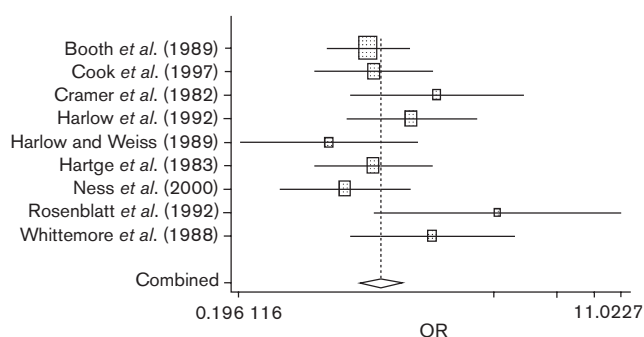
The report by Harlow *et al.* (1992) also represents a potential problem for statistical pooling as the cases in this instance were all patients with ‘borderline ovarian tumors’. The exact nature of borderline ovarian tumors in terms of a relationship with their invasive counterparts remains unclear, with some data suggesting differences in epidemiology and etiology (Riman *et al.*, 2001). Whether borderline tumors are precursors of invasive cancers or a separate disease entity is a matter of debate. We therefore recalculated a summary relative risk without inclusion of data from the study by Ness *et al.* (2000). This gave a

relative risk of 1.09 with a 95% confidence interval of (0.84–1.41), a non-statistically significant result.

All studies except that of Hartge *et al.* (1983) are full research reports with the study by Ness *et al.* (2000) published as a ‘Letter to the editor’. Publication in this format is potentially problematic owing to issues related to the ‘quality’ of the presented data. Letters to the editor normally do not undergo the same type of editorial scrutiny as full research papers. In addition, by their nature, letters are brief notes with limited details presented, precluding rigorous evaluation of methods, results and associated conclusions. In order to address these issues, we dropped the study by Hartge *et al.* from the pooled analysis and, again, recalculated a summary relative risk. This gave a relative risk of 1.07 with a 95% confidence interval of 0.82–1.40. Again, this represents a non-significant finding.

In a prior meta-analysis (Huncharek *et al.*, 2003), we demonstrated a possible bias among studies examining the perineal talc use/ovarian cancer association based on the source of cases. That is, our study suggested that population-based studies may spuriously show a causal association secondary to exposure misclassification to a ‘treatment effect’ among population-derived cases. Some patients with ovarian cancer will undergo treatment with radiation, chemotherapy and/or surgery. Side effects from treatment may prompt talc use among some of these individuals. Patients may not always make the distinction between pre-diagnosis and post-treatment use. Exposure misclassification among ‘prevalent’ cases may cause a spurious finding of an association when none, in fact, exists. We therefore recalculated the summary relative risk excluding the studies by Cook *et al.* (1997) and Harlow and Weiss (1989) as these were the only two reports that utilized population-derived cases and controls. The resultant relative risk was 1.15 with a non-statistically significant odds ratio of 0.87–1.53.

Fig. 1



Forest plot of summary relative risk derived by pooling all available studies using adjusted odds ratios (OR).

Furthermore, this suggests no association between talc use and increased ovarian cancer risk. In fact, if data from the studies by Cook *et al.* (1997) and Harlow and Weiss (1989) are statistically pooled, the summary relative risk is 0.67 with a non-significant confidence interval (i.e. 0.34–1.35). The fact that the population-based relative risk is in the opposite direction (i.e. favoring a protective effect for talc) to that shown in the other case-control studies, further supports the existence of bias in these analyses.

Another methodological consideration is the fact that the definitions of the control groups used across all nine studies are not completely comparable. Some reports defined controls as ‘never having used talc’ (e.g. Ness *et al.*, 2000), while others used controls defined as not

having used talc on diaphragms (e.g. Cook *et al.*, 1997). We therefore calculated crude odds ratios and 95% confidence intervals using data supplied in the available studies and recalculated a summary relative risk to ensure that the analysis using adjusted odds ratio was not spurious (Table 2). The resultant relative risk was 0.86 (0.59–1.40) (see Fig. 2), a non-statistically significant result suggesting no association between talc use on diaphragms and increased ovarian cancer risk (see Fig. 2). Of note, the test for heterogeneity for this latter analysis gave a value for Q of 7.20 with a P value of 0.52.

Discussion

Talc is an important industrial mineral for a number of reasons including its resistance to heat, electricity and acids and its relatively low price. It is used in many commercial applications because of its lamellar platy nature, softness, whiteness, chemical inertness, high melting point and hydrophobic features, among others. For instance, talc is used in the plastic industry owing to its inertness, superior electrical and thermal resistance and its ability to improve the quality of plastic surfaces. It also finds application in the paint industry to increase the

smoothness of paint products and in paper manufacturing to reduce the usage of expensive whitening agents because of its high brightness.

Mineral talc is a magnesium silicate hydroxide belonging to the mineral class, silicate and subclass phyllosilicate. It belongs to the clay mineral group, an important subgroup within the phyllosilicates that contain large percentages of water trapped between the silicate sheets. Clay minerals are divided into four major groups: the kaolinite group, the montmorillonite/smectite group, the illite group and the chlorite group. Talc is a member of the montmorillonite/smectite group along with pyrophyllite, vermiculite, saunonite, saponite and nontronite.

Talc also forms pseudomorphs, that is false shapes, of other minerals, replacing them on an atom by atom basis. For instance, talc forms pseudomorphs of quartz, pyroxene, olivine and amphiboles. In nature, it can also be found in association with a number of other minerals, such as serpentine, quartz, olivine and biotite.

In 1982, Cramer *et al.* (1982) published a case-control study suggesting an association between cosmetic talc use on the perineum and increased ovarian cancer risk. Women dusting the perineum with talc or dusting sanitary napkins showed a near doubling of ovarian cancer risk. Unfortunately, in addition to a number of methodological limitations plaguing this report (e.g. only 45% of eligible controls participating), it is important to point out the flawed premise on which it is based. Cramer *et al.* (1982) cite the 'chemical relationship between talc and asbestos' as a major reason for assuming that talc may also be a human carcinogen and that '...the mineral talc is a specific hydrous magnesium silicate chemically related to several asbestos group minerals and occurring in nature with them'.

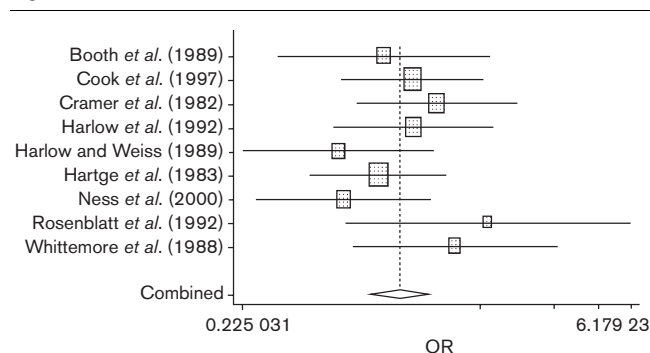
The above-cited justification for the Cramer *et al.* (1982) study and subsequent work examining a possible cosmetic talc/ovarian cancer link is misguided for a number of reasons. Despite the fact that talc and various forms of asbestos are silicates, they are structurally distinct and belong to different mineral groups and subgroups. That is, amphibole minerals (e.g. tremolite) are inosilicates while talc is a member of the silicate subclass phyllosilicate and the group, clay or montmorillonite/smectite. While serpentines, including serpentine asbestos, are also phyllosilicates, serpentine minerals belong to the kaolinite-serpentine group. The asbestos varieties of serpentine are structurally different from other members of the serpentines in that their brucite layers and silicate layers bend into tubes that produce fibers. Non-fibrous serpentine does not have carcinogenic properties and it is clear that the physical structure of serpentine asbestos is responsible for its disease-causing

Table 2 Crude odds ratios and 95% confidence intervals for included studies

Study (year)	Crude OR	95% CI	Variance	Weight
Booth <i>et al.</i> (1989)	0.75	0.33–2.02	0.175	5.70
Cook <i>et al.</i> (1997)	0.96	0.52–1.76	0.097	10.2
Cramer <i>et al.</i> (1982)	1.18	0.59–2.35	0.125	7.99
Harlow <i>et al.</i> (1992)	0.97	0.49–1.92	0.121	8.24
Harlow and Weiss, 1989	0.51	0.22–1.13	0.184	5.43
Hartge <i>et al.</i> (1983)	0.72	0.40–1.30	0.090	11.1
Ness <i>et al.</i> (2000)	0.53	0.25–1.13	0.147	6.80
Rosenblatt <i>et al.</i> (1992)	1.82	0.55–6.34	0.373	2.68
Whittemore <i>et al.</i> (1988)	1.38	0.57–3.28	0.204	4.91

OR, odds ratio; CI, confidence interval.

Fig. 2



Forest plot of summary relative risk derived by pooling all available studies using crude odds ratios (OR).

potential, not its atomic constituents. It simply does not follow, therefore, that one should assume that talc is carcinogenic simply because it is a silicate and a member of the phyllosilicate subgroup. Structure dictates toxicity/carcinogenicity, not chemical composition.

It is true that in nature, mineral talc can be found in association with both serpentine and amphibole minerals, including the asbestos varieties. It is crucial to understand that the carcinogenic potential of asbestos is well known and abundantly documented in the medical and epidemiological literature (Huncharek, 1986; Mossman and Gee, 1989). Cramer *et al.*'s argument suggesting that pure talc is carcinogenic is based solely on 'guilt by association' rather than on scientific fact. If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogenic effect as it contains a known carcinogen. To then suggest that talc is also carcinogenic simply owing to the fact that it is sometimes found in association with various asbestos minerals in nature is not logical. This reasoning ignores a large body of data regarding the mineralogy of silicates and fails to acknowledge the lack of supporting biological or in-vitro data documenting any carcinogenic potential of pure talc (i.e. uncontaminated by asbestos). A commercial product containing asbestos-contaminated talc could certainly pose a health risk and although prior to the mid-1970s some consumer talc products did, in fact, contain such contamination, the carcinogenic entity is asbestos, not talc (Rohl *et al.*, 1976). It is important to note that since that time, talc product manufacturers voluntarily ensured that such products are asbestos free. Despite this fact, even some recent studies looking at the perineal talc dusting/ovarian cancer risk connection show a weak association (e.g. Mills *et al.*, 2004), further suggesting a spurious finding.

Other evidence that indicates that talc and asbestos have dissimilar biological properties is the fact that talc has been used for decades as a sclerosing agent for both benign and malignant pleural effusions (Viskum *et al.*, 1989). Long-term follow-up studies of these patients have not shown even a single case of lung cancer or mesothelioma resulting from introduction of talc to the pleural cavity (Viskum *et al.*, 1989; Shaw and Agarwal, 2004). Epidemiological studies of talc miners and millers also fail to demonstrate an increased cancer risk (Rubino *et al.*, 1976; Gamble, 1993). In-vivo implantation and injection using asbestos of various types, in contrast, unequivocally induce tumors in experimental animals (Huncharek, 1986).

Despite the above-noted problems, the idea that cosmetic talc poses a possible ovarian cancer risk persists. As reviewed in the present paper and elsewhere (Richardson *et al.*, 1985; Tortolero-Luna and Mitchell,

1995) numerous investigators have examined this possible relationship in a variety of case-control studies and at least one cohort study (e.g. Gertig *et al.*, 2000). Most of these categorized talc use as 'ever versus never' used while others further stratified by particular types of use, for example, perineal dusting, sanitary napkin dusting, condoms, etc. Results differ across studies, with some showing no association (Rosenblatt *et al.*, 1992) while others suggests a 'weak effect' (Purdie *et al.*, 1995), that is odds ratios below 1.5.

In addition to the obvious problems with the premise put forth by Cramer *et al.* (1982) and others, validity of the weak effect shown in a number of other epidemiological studies also remains questionable. The major weaknesses of the existing database include (Boger-Meigiddo and Weiss, 2005) the relatively small sample size of most reports, which limits the statistical power to detect an effect (Richardson *et al.*, 1985), the lack of consistent positive association across studies (Baker and Piver, 1994), the absence of a demonstrable dose-response relationship (Daly and Obrams, 1998), the lack of supporting evidence of talc carcinogenicity from animal or in-vitro analyses (Tortolero-Luna and Mitchell, 1995) and the possible presence of uncontrolled confounding producing a spurious positive association. In fact, some of the available observational studies show an inverse dose-response (Ness *et al.*, 2000) that weighs against a causal association. In addition, no plausible biological mechanism capable of explaining how talc could induce ovarian malignancies exists.

In a study, Heller *et al.* (1996) examined talc particle counts in ovarian specimens from 24 women undergoing incidental oophorectomy and compared these counts with reported frequency and duration of talc use. The study sought to examine the hypothesis of a dose-related risk of epithelial ovarian cancer with perineal talc exposure. Women were considered 'exposed' if they reported talc application to undergarments or directly to the perineum. Talc was detected in all ovaries by either polarized light or electron microscopy. No relationship was found between cosmetic talc burden in healthy ovarian tissue and lifelong perineal talc dusting determined by either microscopic methods. This study raises further questions regarding whether reported associations between perineal talc exposure and ovarian tumors in observational studies reflects a carcinogenic action of talc. The validity of these epidemiologic associations has also been questioned because it is unknown whether talc dust in the perineal area can actually penetrate the female reproductive tract and then translocate to the ovaries against physiological forces working in the opposite direction. The work of Heller *et al.* clearly brings this into question.

Although the epidemiological literature focuses primarily on external perineal exposure to talc, a more valid

assessment of the 'talc hypothesis' would appear to be provided by examining the ovarian cancer risk associated with talc dusting of diaphragms. This particular use of talc results in direct female reproductive tract exposure. Although data on the use of talc-dusted diaphragms have been reported in some epidemiological studies, this literature fails to garner the attention devoted to perineal dusting and no systematic evaluation of this particular literature is available. This probably reflects the fact that perineal dusting is a more common practice than dusting contraceptive diaphragms. Nonetheless, exposure via this latter route is, intuitively, a better 'model' for testing whether talc represents a risk factor for ovarian cancer as the exposure is directly to the female genital tract. Consequently, we performed the above-detailed meta-analysis pooling all available published data on this topic.

Using accepted meta-analytic techniques our analysis was unable to demonstrate any increased risk of ovarian cancer associated with use of talc-dusted diaphragms. Despite performing a number of sensitivity analyses to test the robustness of our findings, the pooled data from over 5000 cases and controls failed to show a positive association. In some studies, the odds ratio was calculated based on an inappropriate control group; for example, individuals who reported no exposure to any talc. For these studies, the crude odds ratio was recalculated based on women who never used talc-dusted diaphragms as the reference group. This summary relative risk was also statistically non-significant.

In summary, our present report, along with our prior meta-analysis pooling data from studies examining the possible ovarian cancer risk associated with perineal talc dusting (Huncharek *et al.*, 2003), does not provide evidence of a causal relationship. In the context of 'weak associations', many sources of bias and uncontrolled confounding can contribute to the finding of a spurious association. Recall bias in case-control studies, lack of a demonstrated dose-response in many published analyses, lack of a coherent biological mechanism for possible talc carcinogenicity and lack of supporting animal or in-vitro data demonstrating the carcinogenic potential of talc all argue against a causal relationship. These limitations and inconsistencies have also been discussed in detail elsewhere (Wehner, 1994; Muscat and Barish, 1998). As ovarian cancer remains a major cause of cancer-related morbidity and mortality in the United States, further work is needed to clearly define modifiable risk factors in an attempt to improve disease prevention.

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Exhibit 52

Perineal use of talc and risk of ovarian cancer

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ABSTRACT

Ovarian cancer is one of the most common gynaecological neoplasms, especially in industrialised countries. The aetiology of the disease is not well understood, except that inherited mutations in the breast cancer genes BRCA-1 and BRCA-2 account for up to 10% of all cases,¹ and child-bearing, oral contraceptive use and breast-feeding reduce the risk.² Some environmental exposures, notably talc and asbestos, have been suspected as ovarian carcinogens.

Talc refers to both mineral talc and industrial products that contain mineral talc. Mineral talc occurs naturally in many regions of the world and is valued for its softness, platyness, and ability to absorb organic matter. Mineral talc occurs naturally in a platy (flat) form, but may also occur as asbestiform fibres, which describes its physical form and does not imply the presence of asbestos. The purer forms (approximately 90% mineral talc) are used for cosmetic and hygiene products including baby powders and feminine hygiene products. Perineal use of cosmetic talc is a common practice in the United Kingdom, North America, Australia and some other countries. To our knowledge accurate estimates of prevalence of use of cosmetic talc are not available. However, the use for female hygiene of body powders, baby powders, talcum powders and deodorising powder, most of which contain cosmetic talc in varying amounts, has been reported to be as high as 50% in some countries.³

From pathological studies it is known that particles and fibres that enter the body can migrate to distant organs. For instance, asbestos fibres have been found in ovaries from women exposed to asbestos.^{4,5} Analogously, following perineal application, talc particles can migrate from the vagina to the peritoneal cavity and ovaries.⁶ A majority of women experience retrograde menstruation⁷; this suggests a mechanism by which talc particles can travel through the female reproductive tract to the ovaries. Furthermore, epidemiological studies have shown decreased risks of ovarian cancer after tubal ligation and/or hysterectomy, suggesting that removing a pathway by which carcinogenic substances can reach the ovaries reduces the risk.^{8,9}

The association between talc use in the perineal region and ovarian cancer was investigated in one cohort study,¹⁰ and 20 case-control studies.^{11–30} In the cohort study, arguably the strongest study because of its partly prospective ascertainment of exposure, there was no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined. The various case-control studies provided indications of either a significant excess risk (10 studies) or non-significant excess risk or

null (10 studies), with odds ratios (ORs) ranging from 1.0 to 3.9. None of the studies reported relative risks below 1.0. The population-based case-control studies,^{11 15–17 20–26 28–30} included studies with 112–824 ovarian cancer cases, and had odds ratios ranging from 1.1 to 3.9 (fig 1). The hospital-based case control studies^{12–14 18 19 27} included studies with 77–462 cases, and reported odds ratios between 1.0 and 2.5. Pooled odds ratios were calculated by fixed effects model. As shown in figure 1 pooled ORs were 1.40, 1.12 and 1.35 for population-based, hospital-based and all case control studies combined, respectively. Some studies^{13 14 22 23 26 28} tried to assess exposure-response associations, in terms of frequency of use or length of use in years but found no clear trend.

Methodological factors such as recall bias should always be considered in case-control studies. It could have been a problem had there been widespread publicity about the possible association between use of body powder and cancer. The International Agency for Research on Cancer (IARC) working group considers that there has not been widespread public concern about this issue and therefore considers it unlikely that such a bias could explain the consistent findings. Another source of recall bias could result from the fact that women with the cancer tend to remember or over-report their use of body powder. The influence of this type of recall bias cannot be ruled out.

Eight of the population-based case-control studies^{11 16 22–24 26 28 29} were identified, by the IARC working group as being most informative in terms of size of the studies, whether the studies were population-based, participation rates and adjustments of confounding variables. The selected studies included at least 188 cases and had participation rates ranging from 60% to 75%. Among these eight studies, the prevalence of perineal use of talc-based body powder among controls ranged from 16% to 52%. The relative risks of ovarian cancer among body powder users were homogeneous across this set of eight studies, each of which indicated a 30–60% increase in risk. Among the other 12 case-control studies, most also reported relative risks of this magnitude or higher.

Information on talc use in infancy is generally insufficient in the case-control studies. However, in one study the exposure to baby powder was reported by 42.2% of the cases and 40.5% of the controls.¹⁵ In several of the other studies patients were asked about age at first use of perineal talc, as an indicator for use in infancy or other periods of life.

Only four case-control studies^{16 23 29 30} and one cohort study¹⁰ provided results by histological type. In four of these studies, in particular the cohort study, there were hints of higher risks of serous tumours related to talc exposure.

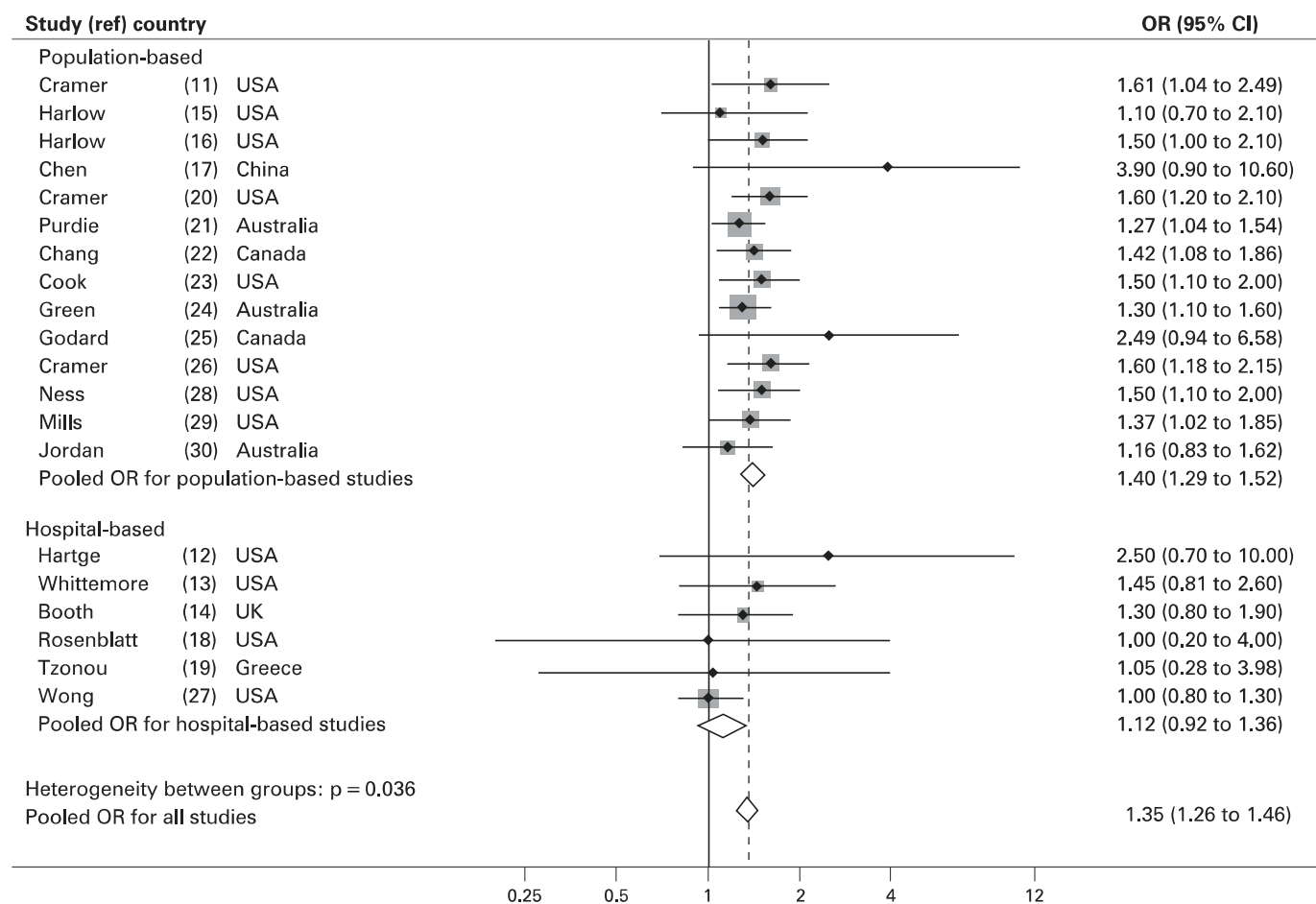


Figure 1 Results from case-control studies contributing data on perineal talc use and ovarian cancer. Results are presented as odds ratios (ORs) and their corresponding confidence intervals (95% CIs) and represented by squares and lines, respectively. Results are separated in 14 population-based and six hospital-based case-control studies. Pooled ORs for all population-based studies combined and all hospital-based studies combined are given. OR pooling by fixed effect models (Mantel-Haenszel method).

Before 1976, talc was to some extent contaminated with asbestos, so that the early studies relating talc to ovarian cancer may have been confounded by the asbestos.³¹ However, the association between talc exposure and ovarian cancer is as strong in recent studies,^{28–29} as in earlier ones, diminishing the likelihood that all these results are influenced by contamination of talc by asbestos.

To summarise the evidence in favour of an association, a very large number of studies have found that women who used talc experienced excess risks of ovarian cancer; some results were statistically significant and some were not. There was some indication in the cohort study of an increase in serous tumours. The evidence of talc migrating to the ovaries lends credibility to such a possible association. The main epidemiological evidence against the association is the absence of clear exposure-response associations in most studies, as well as the absence of an overall excess risk in the cohort study.

On balance, the epidemiological evidence suggests that use of cosmetic talc in the perineal area may be associated with ovarian cancer risk. The mechanism of carcinogenicity may be related to inflammation.³²

The carcinogenicity of non-asbestiform talc was assessed by a monograph working group at IARC in 2006.³³ After considering biases and possible confounding factors, the IARC working group concluded that the epidemiological studies provided

limited evidence for the carcinogenicity of perineal use of talc-based body powder, and classified this use as possibly carcinogenic to human beings (that is, group 2B).³⁴

PROPOSAL: TO RESEARCH COMMUNITY

The current body of experimental and epidemiological evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk. Experimental research is needed to better characterise deposition, retention and clearance of talc to evaluate the ovarian carcinogenicity of talc.

The majority of the epidemiological studies carried out so far have been among American women. It would be instructive to seek evidence in other countries where perineal use of talc has been common.

While there has been some efforts to measure the degree of use, these have mainly been measured simply as the reported years of use. It is possible that the ostensible lack of exposure response trends is the result of crudeness of the exposure metric used. Therefore, it is important that future studies, irrespective of study design, devote some effort to better assessment of exposure. The use of body powders should be assessed both in terms of calendar time and age of the subject. Subjects should be asked about lifetime use, including age at initial use (infancy, childhood, teenager years, adulthood), age at which they stopped using such powders, gaps in the lifetime period of use

What this study adds

- ▶ Epidemiological evidence suggests that use of cosmetic talc in the perineal area may be associated with ovarian cancer risk. The IARC has classified this use of talc as possibly carcinogenic to human beings (group 2B).
- ▶ The mechanism of carcinogenicity may be related to inflammation. This paper focus on the high degree of consistency in the studies accomplished so far, and what should be the focus in future studies.

and frequency and nature of use (daily, during certain seasons of the year, only while menstruating). Another important question is whether the use of body powder was before or after tubal ligation or hysterectomy.

Individuals' answers to questions about use of brand names over time may be unreliable, and therefore, in future studies, investigators should try to ascertain, either from government or industry sources, the composition of the powders used in different time periods by different brand names and, in particular, to ascertain whether the exposure may have included some contamination by asbestos and also whether the exposure was to talc or a non-talc product. Statistical analyses should attempt to assess risk separately for the categories of powders: talc containing asbestos, talc not containing asbestos, non-talc product. Further, exposure metrics should take into account the age, duration and intensity of exposure. As well as analyses for all ovarian tumours combined, there should, if possible, be analyses by histological subtype and by invasiveness of the tumour.

While it would not be reasonable to envisage establishing a costly long-term prospective cohort study just to study this association, any long-term cohort study that is being set up to study cancer among women should collect information about talc use if the study is being conducted in a country where such use has been widespread.

In summary, future studies should focus on seeking evidence in talc-exposed female populations worldwide, collecting reliable information on age at initial use of body powder, exposure assessments and dose response associations.

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Exhibit 53

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Genital use of talc and risk of ovarian cancer: a meta-analysisBerge, Wera^a; Mundt, Kenneth^b; Luu, Hung^c; Boffetta, Paolo^d**Author Information**^aFaculty of Medicine, University of Dresden, Dresden, Germany^bRamboll Environ, Amherst, Massachusetts^cUniversity of South Florida College of Public Health, Tampa, Florida^dIcahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, USA

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Abstract

Some epidemiological studies suggest an association between genital use of talc powders and increased risk of ovarian cancer, but the evidence is not consistent. We performed a meta-analysis of epidemiological studies to formally evaluate this suspected association. A systematic search was conducted in Medline, Embase, and Scopus, leading to the identification of 24 case-control studies and three cohort studies. In the meta-analysis, we used a random-effect model to calculate summary estimates of the association between genital use of talc and occurrence of ovarian cancer. We assessed potential sources of between-study heterogeneity and presence of publication bias. The summary relative risk (RR) for ever use of genital talc and ovarian cancer was 1.22 [95% confidence interval (CI): 1.13–1.30]. The RR for case-control studies was 1.26 (95% CI: 1.17–1.35) and for cohort studies was 1.02 (95% CI: 0.85–1.20, $P_{\text{heterogeneity}}=0.007$). Serous carcinoma was the only histologic type for which an association was detected (RR: 1.24; 95% CI: 1.15–1.34). There was a weak trend in RR with duration and frequency of genital talc use. This meta-analysis resulted in a weak but statistically significant association between genital use of talc and ovarian cancer, which appears to be limited to serous carcinoma with suggestion of dose-response. The heterogeneity of results by study design however, detracts from a causal interpretation of this association.

Introduction

With over 22 000 new cases diagnosed and about 14 000 deaths every year in the USA alone, ovarian cancer ranks as the fifth as a cause of neoplastic death among women. It accounts for more deaths than from any other cancer of the female reproductive system, although incidence numbers decreased since the mid-1980s ([American Cancer Society, 2016](#)). Most ovarian cancers are detected at a later stage and have limited prospects of cure. This is mainly because of the lack of a screening method for its detection at an early stage and resistance against chemotherapy. The etiology of the disease is not fully understood, although researchers have identified several risk factors, including a family history of ovarian or breast cancer, advanced age, white race, nulliparity, obesity, education level, and endometriosis ([Kim et al., 2014](#)). In addition, breast feeding, tubal ligation, and oral contraceptive use have been reportedly associated with reduced risk ([Webb et al., 2008](#)). Ovarian cancer is a heterogeneous disease that comprises four major histologic types; serous carcinoma is the most common form (50%), followed by mucinous, endometrioid, and clear cell carcinoma. Each type, with the exception of clear cell carcinoma, is divided into grades of malignancy ([Wang et al., 2005](#)). On the basis of limited data, there appears to be some heterogeneity in risk factors for specific histologic types ([Chiaffarino et al., 2007](#); [Gates et al., 2010](#)).

An association between exposure to asbestos and increased risk of ovarian cancer has been reported ([Reid et al., 2011](#)), but it remains unclear whether this might reflect misclassification of peritoneal mesothelioma, a disease linked to high exposure to asbestos, or direct action of asbestos fibers on the ovary ([Merino, 2010](#)).

Talc is a naturally occurring mineral that is commonly used in bath and body powders as well as other cosmetic products. Talc naturally occurs as soft crystals that give it a soft, slippery feel, absorbency, softness, and resistance to clumping. It is often applied to sanitary napkins, condoms, or underwear, as well as directly to the genital area. To our knowledge, accurate estimates of prevalence of cosmetic talc use in the genital area are not available. However, the use of powders for female hygiene, including body or deodorizing powders containing cosmetic talc has been reported to be as high as 50% in some regions ([International Agency for Research on Cancer \(IARC\), 2010](#)), including parts of North America, Australia, and the UK.

Since 1982, when the first case-control study reported an association between genital talc and ovarian cancer, interest in genital talc use and risk of ovarian cancer has grown ([Cramer et al., 1982](#)). The use of talcum powder in the genital area had been suggested as a potential risk factor for ovarian cancer based, in part, on a possible structural analogy with asbestos ([Cramer et al., 1982](#)) or the possible contamination by asbestos of some talcum powders in the past ([Cralley et al., 1968](#)). However, the structural similarities between asbestos minerals in the crystalline fiber form (i.e. asbestos habit) and structures seen microscopically in talcum that resemble fibers such as 'ribbons' of talc crystals or cleavage fragments of talc or other minerals, are few. Furthermore, talcum powders for domestic use in the USA have been virtually asbestos-free since the 1970s ([Rohl et al., 1976](#)).

Several more recent case-control studies have reported associations between ovarian cancer and self-reported genital talcum powder use. However, the association between talc use and ovarian cancer risk reported in case-control studies has not been limited to studies in which genital talcum powder use occurred before cosmetic products were known to be asbestos-free. It has been suggested that talcum powder may be directly carcinogenic to the ovaries, provided that talc particles may be able to travel through the female reproductive system to the ovaries ([Heller et al., 1996](#)). In one study, talc-like particles were detected more frequently in ovarian tumors than in normal human ovarian tissue, although the authors of this study emphasized that this study could not determine whether these particles actually caused the malignancy ([Henderson et al., 1979](#)).

Results of epidemiological studies reported during the last three decades have not been consistent ([Huncharek et al., 2007](#); [Terry et al., 2013](#); [Houghton et al., 2014](#)). It remains unclear whether a statistical association exists, and, if so, whether it can be interpreted as reflecting some form of bias or a causal relationship. We performed a systematic review and meta-analysis aiming at providing stronger evidence in favor or against the hypothesis of a causal association between genital talc use and risk of ovarian cancer.

Methods

We performed a systematic review and meta-analysis on the association between genital talc powder use and the risk of ovarian cancer. Our work was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines ([Liberati et al., 2009](#)). A study protocol was developed in advance, outlining the procedure and methods (available upon request).

Search strategy

A series of literature searches was conducted in June 2016 using the electronic databases Medline (by PubMed), Embase, and Scopus. There was no limitation on year of publication. We included relevant studies that met the following criteria: papers had to be published in peer-reviewed journals as an original report; had to present novel information on the relation between genital powder use and ovarian cancer, and had to be written in English, German, Italian, French or Spanish. As there are different types of genital powders, we defined genital powder as any type of powder that is applied to the genital, rectal or perineal area, such as talc, baby, deodorizing, cornstarch, or powder of unknown type. We excluded review articles, abstracts, editorials or letters to the editor not including original data, and other studies not meeting the selection criteria.

The following keywords were used for the searches on Medline and Scopus: 'perineal powder' or 'talcum powder' or 'genital powder' and 'ovarian cancer.' For Embase we used the following combination of keywords: 'perineum' or 'talc' and 'ovarian cancer.' In addition, all references cited in the identified papers and reviews were hand-searched for potentially relevant studies that were not captured by the electronic database search.

Study selection

Titles and abstracts were examined independently by two of the authors (W.B., P.B.). Duplicates and irrelevant references were eliminated. In case of disagreement or doubt the abstracts or articles were discussed until consensus was reached. In case of overlap of results between publications the selection of results was on the basis of the largest population or most detailed analysis, resulting in the exclusion of some publications which were superseded by more recent reports ([Harlow et al., 1992](#); [Cramer et al., 1999](#); [Pike et al., 2004](#)).

Data extraction

All data of the included studies were extracted by one author (W.B.) and checked by another author (P.B.). Possible disagreements were discussed and solved.

The following data were extracted from each study for the meta-analysis: first author and publication year; study design; study region; period of enrollment; survey instrument; assessment of ovarian cancer; age range; numbers of women with ovarian cancer and those without in case-control studies; numbers of cases of ovarian cancer, sample size and a number of person-years in cohort studies; adjustment for potential confounding factors; outcome by talc exposure (yes/no); duration (years); frequency (times/week); timing of use (early/late); type of talc exposure (sanitary napkin, diaphragm, genital deodorant, cornstarch, use by the partner); endometriosis; surgery (hysterectomy and/or tubal ligation); number of powder applications; characteristics of the participants; and tumor histology and behavior.

Quality assessment

Every included article was scored for its quality according to a standardized checklist. We used the Newcastle–Ottawa Scale (NOS) case-control checklist and the NOS cohort study checklist for both study types, respectively ([Stang, 2010](#)). The NOS assesses three dimensions of quality: selection, comparability, and exposure (for a case-control study) or outcome (for a cohort study). It assigns a maximum of four points for selection, two points for comparability, and three points for exposure or outcome. Studies with at least seven points were considered of high quality (Supplementary Table 1, Supplemental digital content 1,

<http://links.lww.com/EJCP/A138>

and Table 2, Supplemental digital content 2,

<http://links.lww.com/EJCP/A139>

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Statistical analyses

The measure of association of interest was the relative risk (RR) for prospective cohort studies, and the odds ratio (OR) for the case-control studies, with corresponding 95% confidence intervals (CIs). The main meta-analysis compared ever versus never use of genital talc; additional analyses addressed use of powder on sanitary napkins and diaphragms, two potential sources of talc exposure. If results were reported only by categories of exposure, indicators of ever talc use were derived using fixed-effect meta-analyses. Risk estimates were abstracted from each study for comparable exposure categories. An overall pooled RR was then estimated, together with its 95% CI, on the basis of individual estimates from each study. Each study was given a weight on the basis of the inverse of the variance of the effect estimate. We pooled data on different exposures when at least four studies provided sufficient data. A random-effects model was used in the meta-analyses comprising multiple studies, because of the heterogeneity in study design and analysis (DerSimonian and Laird, 1986). The I^2 -statistic was used to assess the percentage of between-study variability that is because of heterogeneity rather than chance (Higgins et al., 2003).

Stratified meta-analyses were conducted for ever genital use of talc according to study design (case-control vs. cohort studies), as well as tumor histology and behavior. Because of the fact that cosmetic talc may have been contaminated by asbestos before the 1970s, when voluntary guidelines were adopted, we compared the results on use in an 'early' and in a 'late' period: the exact cut-point varied across the studies but in general referred to 1970 or 1980.

Meta-regression analyses were performed to obtain overall risk estimates for duration (RR for 10-year increase in duration) and frequency of genital talc use (RR for one time/week increase in frequency), for the studies reporting at least three categories of duration or frequency of use. Study-specific slopes were first derived from the natural logarithm of the risk estimates within each study; in a second step the slopes were pooled using a random-effects model.

The presence and extent of publication bias were assessed visually using funnel plots and evaluated statistically using the Egger's test (Egger et al., 1997). A cumulative meta-analysis was also performed by repeating the calculation of the summary RR and CI (on the basis of a random-effects model) each year a new study was published. When an article superseded a previous article from the same study, the results reported in the earlier report were replaced by the new results.

Analyses were performed using the commands *metan*, *gls*, *metafunnel*, and *metabias* of the statistical software STATA, version 14 (StataCorp, 2015).

Results

The process of selection of relevant studies is shown in Fig. 1. The electronic searches resulted in a total of 435 articles, of which 150 overlapped between searches. After the exclusion of the duplicates and the addition of two articles identified through the review of the lists of references of eligible articles, we screened the titles of abstracts of 287 articles, and excluded 227 which appeared not to be relevant. We then reviewed the full text of the remaining 60 articles, and excluded 32 (17 commentaries, reviews or meta-analysis; three letters to the editor without original results, six reports of studies of ovarian cancer without results on talc use, and six articles whose results were superseded by subsequent publications). The remaining 28 articles, comprising three cohort studies, 24 case-control studies, and one pooled analysis of eight of the 24 case-control studies, were included in the review and meta-analysis.

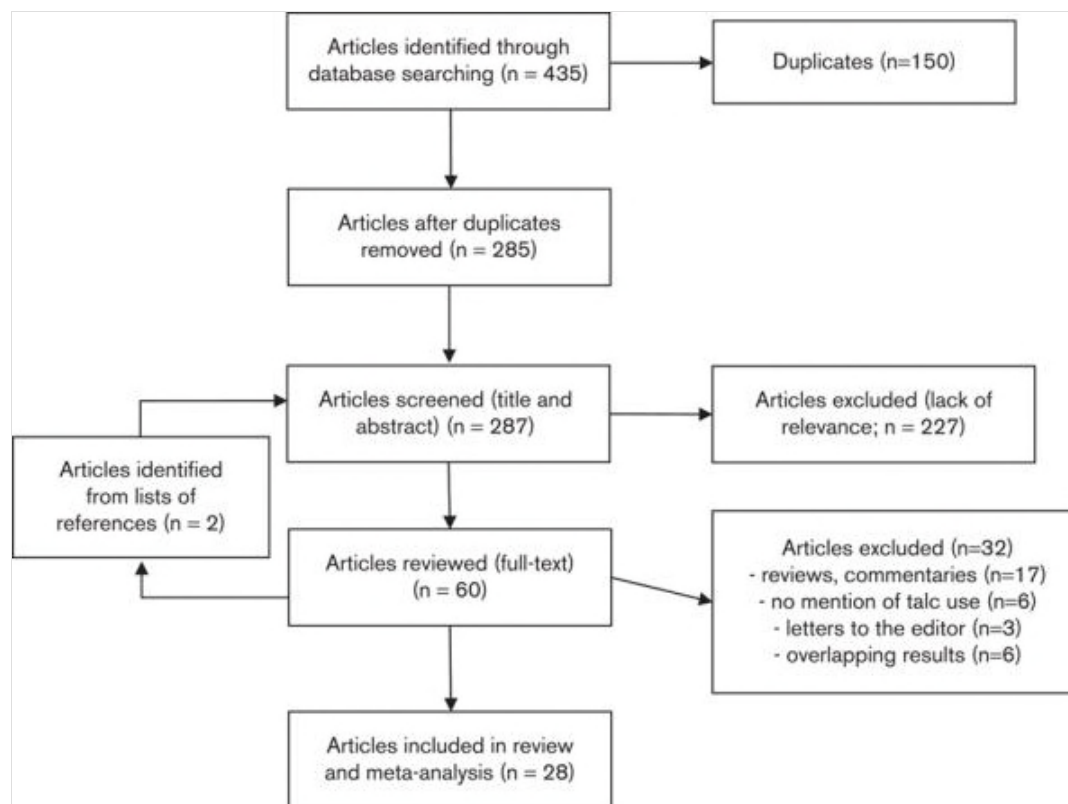


Fig. 1. Flow chart for the selection of studies to include in the meta-analysis.

Table 1 shows selected characteristics of the 28 articles included in the review, which provided the 27 risk estimates included in the meta-analysis [the pooled analysis (Terry et al., 2013) did not provide an independent risk estimate]. For three of the case-control studies included in the pooled analysis (Goodman et al., 2008; Moorman et al., 2009; Lo-Ciganic et al., 2012) results on genital talc use had not been reported in the original publications and were abstracted from the pooled analysis (Terry et al., 2013). Twenty studies were conducted in the USA, two in Australia, two in Canada, one in Great Britain, one in China, and one in Greece. Potential confounding factors including age, parity, history of tubal ligation or hysterectomy, and use of oral contraceptive were adjusted for in most studies, although there were differences in the specific adjustments across studies. Six of the 24 case-control studies were hospital-based with the remainder being population-based.

References	Country	Study type	Age range	N ca/co	Potential confounders	Inclusion in meta-analysis	Overlap between publications
Cramer et al. (1982)	USA	CCC	18-80	215/215	Pa, MS	E, N, D	
Hartge et al. (1983)	USA	HCC	NA	135/171	-	E, D	
Whittemore et al. (1985)	USA	HCC	18-74	188/539	Pa, OC	E, N, D, Du, F	
Booth et al. (1989)	UK	HCC	20-64	235/451	SES	E, F	
Harlow and Weiss (1989)	USA	CCC	20-79	116/158	Pa, OC	E, N, D	
Chen et al. (1992)	China	NA	NA	112/224	Pa, Ed	E	
Harlow et al. (1992)	USA	CCC	18-76	235/239	Pa, Ed, MS, BMI	E, H, B, F, Du, T, N, D	
Rosenblatt et al. (1992)	USA	HCC	All	77/46	-	E, N, D	
Tzonou et al. (1993)	Greece	HCC	<75	189/200	Pa, Ed, BMI, AMe, MS, AFB, Tob, Cor, Alc, Med, HD	E	
Purdie et al. (1995)	Australia	CCC	18-79	824/860	Pa	E	
Cheng and Reich (1997)	Canada	CCC	35-79	453/584	OC, NP, BF, TL, Hys, FH	Du, T, N	Included in Terry et al. (2013)
Cook et al. (1997)	USA	CCC	20-79	313/422	-	E, H, Du, N, D	
Godard et al. (1998)	Canada	CCC	20-84	170/170	-	E	
Wong et al. (1999)	USA	HCC	NA	499/755	Pa, OC, Tob, FH, AMe, MS, Inc, Ed, TL, Hys	E, Du, N	
Noss et al. (2000)	USA	CCC	20-69	767/1367	NP, FH, OC, TL, Hys, BF	E, Du, N, D	
Mita et al. (2004)	USA	CCC	18+	256/1122	OC, BF	E, H, B, F, Du, T	
Goodman et al. (2008)	USA	CCC	18+	367/802	NA	-	
Moorman et al. (2009)	Australia	CCC	18-79	1576/1509	Pa, Ed, OC	Du	Included in Terry et al. (2013)
Lo-Ciganic et al. (2012)	USA	CCC	20-74	1086/1057	-	-	Included in Terry et al. (2013)
Gates et al. (2010)	USA	Cohort	30-55	721/-	Pa, BMI, PA, Tob, FH, BF, OC, TL, Hys, Amp, HRT	E, H, F, N ^a	
Rosenblatt et al. (2011)	USA	CCC	35-74	812/1313	NP, OC	Du, T, N, D	Included in Terry et al. (2013)
Lo-Ciganic et al. (2012)	USA	CCC	25+	902/1802	NA	-	Included in Terry et al. (2013)
Terry et al. (2013)	USA, Canada, Australia	-	-	-	Pa, OC, TL, BMI	E, H, B	Pooled data from Cheng and Reich (1997), Goodman et al. (2008), Moorman et al. (2009), Rosenblatt et al. (2011), Lo-Ciganic et al. (2012), Merritt et al. (2008)
Houghton et al. (2014)	USA	Cohort	50-79	429/-	Pa, OC, HRT, FH, ALB, BMI, Tob, TL	E, H, N, D, Du	
Wu et al. (2015)	USA	CCC	18-74	1701/2391	MS, AMe, HRT, BMI, Inc, Ed, NP, OC, TL, End, FH	E, T ^b	
Cramer et al. (2016)	USA	CCC	18-80	2041/2100	-	E, H, B, F, Du, D	
Gonzalez et al. (2016)	USA, Puerto Rico	Cohort	35-74	164/-	BMI, OC, MS, TL, Hys	E	
Schildkraut et al. (2016)	USA	CCC	20-79	584/745	Pa, Ed, OC, BMI, TL, FH	E, H, Du, F	

N ca/co, number of cases and controls (only cases for cohort studies); AFB, age at first birth; ALB, age at last birth; AMe, age at menarche; AMp, age at menopause; B, tumor history; BF, breast feeding; CCC, community-based case-control study; D, diaphragm use; Du, duration of use; E, ever use; Ed, education; F, frequency of use; FH, family history of breast and ovarian cancer; H, histologic type; HCC, hospital-based case-control study; HD, hair dye use; HRT, hormone replacement therapy; Hys, hysterectomy; Inc, income; Med, use of medications; MS, menopausal status; N, sanitary napkin use; NA, not available; NP, number of pregnancies; OC, oral contraceptive use; Pa, parity; SES, socioeconomic status; T, timing of use; TL, tubal ligation.
^aResults abstracted from Gertig et al. (2000).
^bResults abstracted from Wu et al. (2009).

Table 1 Selected characteristics of the studies included in the meta-analysis

The results of the meta-analysis are reported in Table 2. We used the results reported in the meta-analysis by Terry et al. (2013) for six of the original eight studies (Chang and Risch, 1997; Goodman et al., 2008; Merritt et al., 2008; Moorman et al., 2009; Rosenblatt et al., 2011; Lo-Ciganic et al., 2012), while for the remaining two studies (Cramer et al., 1999; Pike et al., 2004) we used the more extensive results reported in subsequent publications (Wu et al., 2015; Cramer et al., 2016).

	Number of risk estimates	RR	95% CI	p-het
Overall	27	1.22	1.13–1.30	0.02
Study design				
Cohort studies	3	1.02	0.85–1.20	0.2
Case-control studies	24	1.26	1.17–1.35	0.08
Hospital-based case-control studies	6	1.34	1.16–1.51	0.8
Community-based case-control studies	18	1.24	1.13–1.35	0.03
Histology				
Serous carcinoma	13	1.24	1.15–1.34	0.4
Mucinous carcinoma	12	0.96	0.73–1.18	0.8
Endometrial carcinoma	12	1.15	0.91–1.39	0.1
Clear cell carcinoma	8	0.98	0.72–1.23	0.8
Behavior				
Invasive	9	1.20	1.08–1.31	0.2
Borderline	9	1.27	1.09–1.44	0.9
Period of exposure ^a				
Early	5	1.18	0.99–1.37	0.2
Late	5	1.31	1.03–1.61	0.2
Specific sources of talc exposure				
Sanitary napkin	12	1.00	0.84–1.16	0.5
Diaphragm	11	0.75	0.63–0.88	0.8

CI, confidence interval; p-het, *P*-value of test for interstudy heterogeneity; RR, relative risk.

^aCut-points between periods vary across studies but in general refer to 1970 or 1980.

Table 2 Ever use of genital talc – results of meta-analysis

The meta-analysis of all 27 risk estimates for ever use of genital talc yielded a summary RR of 1.22 (95% CI: 1.13–1.30). The forest plot of these results is shown in Fig. 2. When the meta-analysis was stratified according to study design, an association with ever genital talc use was detected in case-control studies (RR: 1.26; 95% CI: 1.17–1.35), but not in cohort studies (RR: 1.02; 95% CI: 0.85–1.20). The *P*-value of the test for heterogeneity of results according to study design was 0.007.

Furthermore, hospital-based case-control studies resulted in a higher summary RR than community-based case-control studies (*P*=0.3, for heterogeneity between the two groups of case-control studies).

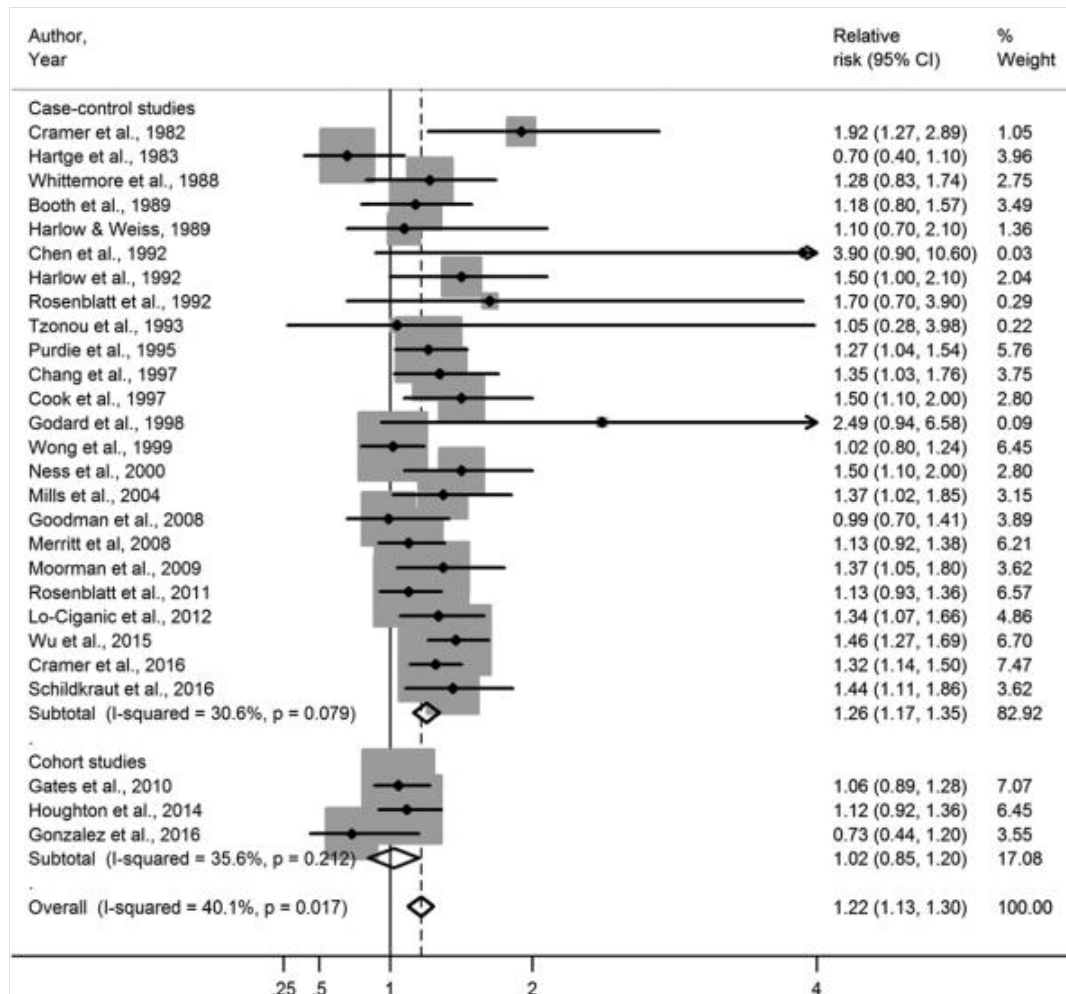


Fig. 2. Forest plot of results on ever use of genital talc and risk of ovarian cancer. CI, confidence interval.

The meta-analysis stratified by tumor behavior did not reveal a difference between results for borderline (RR: 1.27; 95% CI: 1.09–1.44) and invasive ovarian cancer (RR: 1.20; 95% CI: 1.08–1.31). The analysis stratified by histology, however, identified an association between ever genital use of talc and serous carcinoma (RR: 1.24; 95% CI: 1.15–1.34, on the basis of 13 case-control studies and no cohort studies). No significant associations were detected for endometrial (RR: 1.15; 95% CI: 0.91–1.39), mucinous (RR: 0.96; 95% CI: 0.73–1.18) or clear cell (RR: 0.98; 95% CI: 0.72–1.23) carcinomas. The *P*-value of the test of heterogeneity between histologic types was 0.04. Only two cohort studies reported histology-specific results, showing neither a difference between types nor stronger association for serous carcinoma (results not shown in detail). Three of the studies (Mills et al., 2004; Rosenblatt et al., 2011; Cramer et al., 2016) reported results for serous carcinoma stratified by tumor behavior: they did not suggest any difference (RR=1.39, for borderline serous carcinoma; 95% CI: 1.04–1.74; RR: 1.32, for invasive serous carcinoma; 95% CI: 0.97–1.67; *P*_{heterogeneity}=0.5).

Use of talcum powder in the 'early' period showed weakly increased risk of ovarian cancer (RR: 1.18; 95% CI: 0.99–1.37), whereas the RR for use in the 'late' period was slightly higher but less precisely estimated (RR: 1.31; 95% CI: 1.03–1.61). The *P*-value of the test for heterogeneity between groups of studies was 0.37.

Use of sanitary napkins or diaphragms was not associated with an increased risk of ovarian cancer (RR: 1.00; 95% CI: 0.84–1.16; and RR: 0.75; 95% CI: 0.63–0.88, respectively).

We conducted additional analyses after stratifying the studies according to whether the results were adjusted for key potential confounders (use of oral contraceptives and hormone replacement therapy, socioeconomic status/education, BMI; see Table 1 for details), but found no evidence of heterogeneity (results not shown in detail).

The results of the analysis by duration and frequency of genital talc use are reported in Table 3. A 10-year increase in genital talc use was associated with a RR of 1.16 (95% CI 1.07-1.26; 12 studies), whereas the RR for an increase of one application per week was 1.05 (95% CI 1.04-1.07; 7 studies).

	Number of risk estimates	RR	95% CI
Duration (10 years)	12	1.16	1.07–1.26
Frequency (1 time/week)	7	1.05	1.04–1.07

CI, confidence interval; p-het, RR, relative risk.

Table 3 Duration and frequency of use of genital talc – results of meta-analysis

The funnel plot of the results of ever genital talc use is shown in Fig. 3. Visual inspection of the plot suggests no serious publication bias: this conclusion is supported by the result of the Egger test ($P=0.7$). The results of the cumulative meta-analysis (Fig. 4) suggest that after the publication of a few initial studies with inconsistent results, the summary RR stabilized with values in the range of 1.20–1.25.

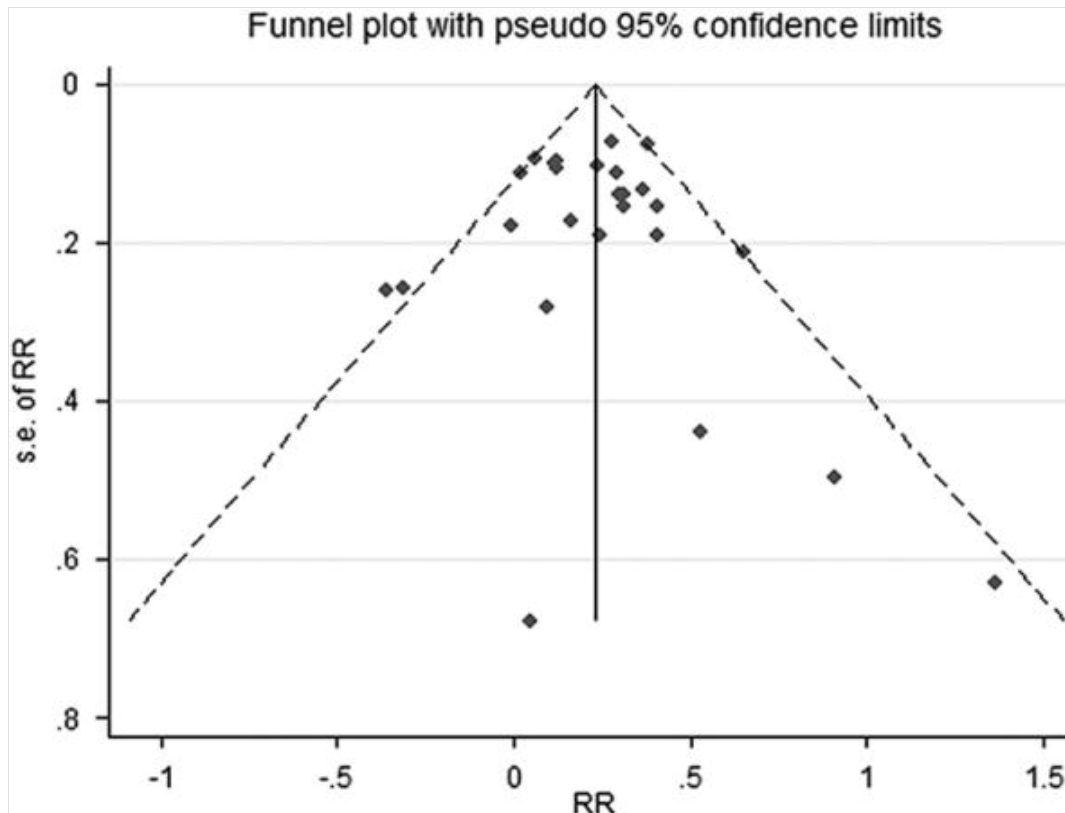


Fig. 3. Funnel plot of results on ever use of genital talc and risk of ovarian cancer. RR, relative risk.

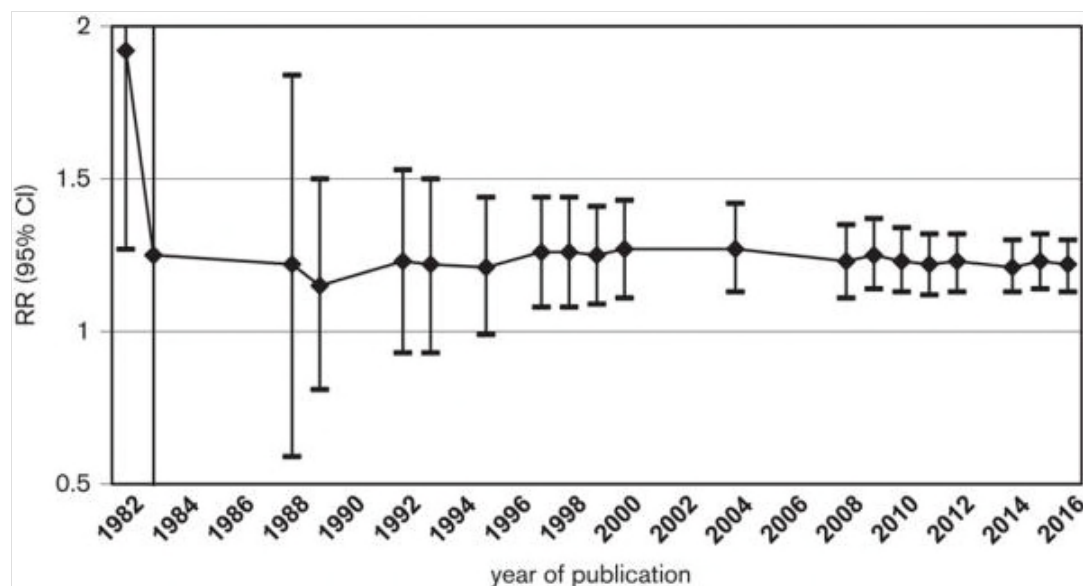


Fig. 4. Cumulative meta-analysis of results on ever use of genital talc and risk of ovarian cancer. CI, confidence interval; RR, relative risk.

Discussion

Ovarian cancer, unless diagnosed and treated early, remains a highly lethal disease and the identification of modifiable risk factors is an important component of the strategy for its control. The primary aim of this meta-analysis was to determine whether talcum powder use in the female genital area is a potential risk factor for ovarian cancer. Previous meta-analyses ([Huncharek et al., 2003](#); [Langseth et al., 2008](#)) were only on the basis of a fraction of currently available studies, and had limited ability to explore potential sources of heterogeneity in results.

This meta-analysis suggests that genital powder use is associated with a small increased risk of developing ovarian cancer; however, this positive association appears to be limited to the serous histologic type, and to case-control studies. This estimate is somewhat lower than that of previous meta-analyses ([Huncharek et al., 2003](#); [Langseth et al., 2008](#)): in our cumulative meta-analysis we confirmed the trend toward lower overall risk estimates as more evidence accumulated.

An important feature of the present meta-analysis is the inclusion of several cohort studies, which enabled an analysis stratified by study design. This analysis provided evidence of heterogeneity of results between the two groups of studies, with an association generally detected in case-control studies but not in cohort studies. It should be noted that the cohort studies included in the meta-analysis comprised a total of 429 cases of ovarian cases exposed to genital talc and 943 unexposed cases: the statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as explanation of the heterogeneity of results.

The fact that the association between genital talc use and risk of ovarian cancer is present in case-control, but not in cohort studies, can be attributed to bias in the former type of studies ([Kopce and Esdaile, 1990](#); [Rothman et al., 2008](#)). Selection bias might have played a role in the results of some of the case-control studies (e.g. those with low response rate, or those hospital-based, which resulted in a nonsignificantly higher summary risk estimate than community-based studies); in addition, information bias from retrospective self-report of talc use is a possible explanation for the association detected in case-control studies. In particular, some of the most recent case-control studies ([Cramer et al., 2016](#); [Schildkraut et al., 2016](#)) have reported particularly strong associations ($RR > 1.4$) for ever use of talc. These results may have occurred at least in part because of participants' knowledge about the latest controversies about talc use and ovarian cancer risk spread by the media ([Muscat and Huncharek, 2008](#)).

The results of the analysis by histologic type of ovarian cancer pointed toward an association with serous carcinoma, but not with the other main types (i.e. endometrial, mucinous, and clear cell carcinoma). Several studies have suggested heterogeneity in risk factors of different histologic types, which are characterized by distinctive molecular and genetic profiles (Kurian et al., 2005; Gates et al., 2010; Gilks, 2010). However, no results are available on whether the association between asbestos exposure and ovarian cancer risk varies by histologic type (Camargo et al., 2011; Reid et al., 2011). The finding that the association between genital talc use and ovarian cancer may vary by histologic type detracts from the hypothesis of report bias as an explanation of the findings of case-control studies, as this type of bias would likely operate for all histologic types of the disease. Caution should however be warranted in the interpretation of these findings, as the test for heterogeneity between groups was of borderline statistical significance, and the evidence for heterogeneity derives only from case-control studies.

The presence or absence of a dose-response is an important aspect to consider in assessing the plausibility of the causal nature of an association observed in a meta-analysis. The number of studies included in the analysis of duration and frequency of genital talc use was not very large, and the modest association between both duration and frequency of use of talc may reflect a true relationship, or recall bias or confounding, and analyses based on larger datasets would be required is a potentially important and novel contribution of this meta-analysis.

We aimed at analyzing the results on genital use of talc according to time-periods; this analysis was limited by different cut-points used by various authors to define time intervals of exposure. In general, however, we were able to distinguish an 'early' and a 'late' period, with the limit between the two running between 1970 and 1980, and we found a statistically significant association only for 'late' use. This result goes against the hypothesis that a stronger association (if any) would be seen among those more likely to have used talcum powders in a time period in which contamination with asbestos fibers was possible (Rohl et al., 1976).

Our study suffers from limitations common to meta-analyses of observational studies: neither the definition of the exposure of interest (genital talc use) nor the strategy for adjustment for potential confounders were fully consistent across studies. Also, there were limitations not specific to our study, including the self-reported information on the main exposure of interest, with no external validation data, the predominance of retrospective case-control studies, and the small number of studies providing results by histologic type or quantitative measures of genital talc use. It is difficult to assess the combined effect of the potential sources of bias, as they might have operated in different directions on the estimate of the association between talc use and ovarian cancer. The stratified analyses we conducted did not point toward the presence of residual confounding (i.e. higher risk estimates for unadjusted compared with adjusted results).

The biological basis and plausibility of a possible carcinogenic effect of talc on the ovaries is still not understood and remains questionable. The similarity of physicochemical characteristics of talc and asbestos has been proposed to explain a carcinogenic effect of the former (Cramer et al., 1982). However, although both talc and various forms of asbestos minerals belong to the family of silicates, they are morphologically distinct. It is the fibrous form of asbestos which determines its carcinogenic potential (Stanton et al., 1981; Huncharek, 1986; Mossman and Gee, 1989). Talc is not fibrous or crystalline (International Agency for Research on Cancer (IARC), 2010), and in-vitro studies have shown that talc is not genotoxic (Wehner, 1994). This is supported by the evidence that exposure to talc not contaminated with asbestiform fibers is not associated with increased risk of lung cancer or mesothelioma in occupational cohorts (International Agency for Research on Cancer (IARC), 2010). The occupational cohorts supporting this conclusion comprise mostly men, and therefore provide no evidence in favor or against the hypothesis of a role of occupational talc exposure as an ovarian carcinogen, but the likelihood that talc could selectively cause ovarian cancer but not lung cancer or mesothelioma at high concentrations in talc miners and millers appears to be low. Furthermore, there is no evidence that occupational exposure to talc, for example, in the pulp and paper industry, entails an increased risk of ovarian cancer (Langseth and Kjaerheim, 2004).

In conclusion, our meta-analysis identified a small but statistically significant association between genital talc use and risk of ovarian cancer; however, this association was limited to the serous histologic type, and to case-control studies. The results by histologic type might argue for specificity of the association, in the absence, however, of a biologic rationale for an effect on serous carcinoma compared with other types. Several aspects of our results, including the heterogeneity of results between case-control and cohort studies, however, do not support a causal interpretation of the association.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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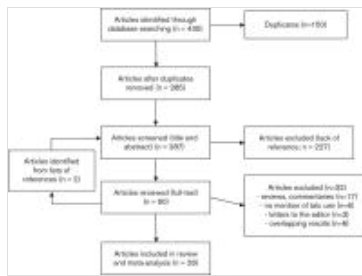
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Keywords: meta-analysis; ovarian cancer; talc

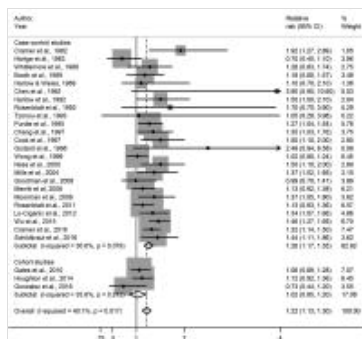
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	Number of risk estimates	RR	95% CI	<i>p</i> -value
Overall	27	1.02	1.13-1.20	0.03
Study design				
Cohort studies	3	1.02	0.85-1.20	0.85
Case-control studies	24	1.26	1.17-1.38	0.00
Hospital-based case-control studies	6	1.34	1.16-1.51	0.00
Community-based case-control studies	18	1.24	1.13-1.35	0.03
Histology				
Squamous carcinoma	13	1.24	1.15-1.34	0.01
Mucinous carcinoma	12	0.98	0.73-1.18	0.88
Endocervical carcinoma	12	1.15	0.91-1.39	0.21
Clear cell carcinoma	6	0.98	0.72-1.23	0.89
Behavior				
Invasive	9	1.20	1.06-1.31	0.01
Borderline	9	1.27	1.00-1.44	0.04
Period of exposure ^a				
Early	5	1.18	0.99-1.37	0.23
Late	5	1.31	1.00-1.61	0.22
Specific sources of tobacco exposure				
Santitas rapin	12	1.00	0.84-1.15	0.98
Diaphragm	11	0.79	0.63-0.98	0.08



	Number of risk estimates	RR	95% CI
Duration (10 years)	12	1.16	1.07-1.25
Frequency (1 time/week)	7	1.05	1.04-1.05

CI, confidence interval; a-het, RR, relative risk.

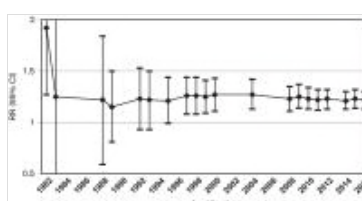
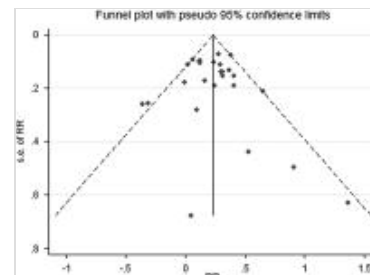


Exhibit 54

Perineal Talc Use and Ovarian Cancer

A Systematic Review and Meta-Analysis

Ross Penninkilampi, and Guy D. Eslick

Background: It has been posited that there is an association between perineal talc use and the incidence of ovarian cancer. To date, this has only been explored in observational studies.

Objectives: To perform a meta-analysis to evaluate the association between perineal talc use and risk of ovarian cancer.

Methods: Studies were identified using six electronic databases. Observational studies involving at least 50 cases of ovarian cancer were eligible for inclusion. We analyzed the association between ovarian cancer, including specific types, and any perineal talc use, long-term (>10 years) use, total lifetime applications, and use on diaphragms or sanitary napkins. A subgroup analysis was performed, stratifying by study design and population.

Results: We identified 24 case-control (13,421 cases) and three cohort studies (890 cases, 181,860 person-years). Any perineal talc use was associated with increased risk of ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). More than 3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) were slightly more associated with ovarian cancer than <3600 (OR = 1.32; 95% CI = 1.15, 1.50). An association with ever use of talc was found in case-control studies (OR = 1.35; 95% CI = 1.27, 1.43), but not cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). However, cohort studies found an association between talc use and invasive serous type ovarian cancer (OR = 1.25; 95% CI = 1.01, 1.55). We found an increased risk of serous and endometrioid, but not mucinous or clear cell subtypes.

Conclusions: In general, there is a consistent association between perineal talc use and ovarian cancer. Some variation in the magnitude of the effect was found when considering study design and ovarian cancer subtype.

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All authors have read the manuscript, agree that the work is ready for submission, and accept the contents of the manuscript.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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Ovarian cancer is the gynecologic cancer associated with the highest mortality in the United States, in 2012 being the fifth highest cause of cancer death in women with 14,404 deaths in that country.¹ The National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) predicts that in the United States, in 2016, there will be 22,280 incidences of newly diagnosed ovarian cancer, and 14,240 deaths caused by ovarian cancer based on age-adjusted data from 2009 to 2013.² The 5-year survival statistics for ovarian cancer are poor, largely because patients usually present with advanced disease, which is less amenable to curative therapy.³ SEER estimates that only 15% of patients present with disease localized to the ovary, which contributes to a 5-year survival of 46.2%.² It is imperative to develop public health programs, which either reduce the incidence of ovarian cancer or detect it at an earlier stage, to reduce the burden of this disease.

Routine pelvic examinations, transvaginal ultrasonography, and tumor markers have been trialed as potential screening tools for ovarian cancer, but are limited in their usefulness. The cancer marker cancer antigen 125 (CA-125, also known as mucin 16) has been found to be elevated in 80% of all ovarian carcinomas, but this falls to 50% in women in which the cancer is localized only to the ovary, where it is most amenable to treatment.⁴ As CA-125 has a low sensitivity and limited specificity, it is not recommended as a screening test for women without clinical symptoms.⁵ Ultrasound has a reasonable sensitivity but poor specificity and positive predictive value, particularly as it is poor at distinguishing between benign and malignant masses.⁶ While the search for an effective screening regimen for ovarian cancer continues, the importance of primary prevention becomes paramount.

Talcum powder is made of talc, a hydrated magnesium silicate, and is used to absorb moisture on the body. Some women choose to dust talc on the perineum, or apply it to diaphragms or sanitary napkins, to reduce friction, keep the skin dry, reduce odor, and prevent rashes. The potential association between perineal talc use and ovarian cancer has been discussed for decades. The first investigation of this association was performed by Cramer et al⁷ in 1982, when the investigators found a relative risk of 1.92 (95% CI = 1.27, 2.89) for ovarian cancer when women either dusted the perineum with talc powder or used it on sanitary napkins. Since this time, there has been substantial interest in and research into this association.

In the present context, the association between talc use and ovarian cancer takes on considerable relevance, as the pharmaceutical and consumer products company Johnson & Johnson has recently had damages levied to the total of US\$717 million against them in five law suits. In these cases, juries decided that the use of talcum powder caused or contributed to the development of the plaintiff's ovarian cancer. The evidence for the association between perineal talc use and ovarian cancer is based on the body of knowledge from observational studies, and most of these have been retrospective case-control studies prone to recall bias. Hence, while perineal talc use has not been shown to be safe, in a similar regard, a certain causal link between talc use and ovarian cancer has not yet been established.^{8,9}

In 2013, a pooled analysis was performed for eight population-based case-control studies, and found a modest increased risk (OR = 1.24) of ovarian carcinoma associated with perineal talc use.¹⁰ In 2007, a meta-analysis was performed of nine observational studies; however, this study only examined the use of talc on contraceptive diaphragms.¹¹ The overall finding of this meta-analysis was that the use of talc on contraceptive diaphragms was not associated with ovarian cancer. Meta-analyses have been performed on this subject before; however, the most recent was in 2008,⁹ and since this time, the results of a number of large case-control studies and two cohort studies^{12,13} have been published. Hence, there is a need to update the literature, particularly considering pending litigation against Johnson & Johnson by other claimants, and Johnson & Johnson's potential plans to appeal the previous decisions. Furthermore, producers of talcum powder products continue to sell these products without any warning labels regarding perineal use and potential associations with ovarian cancer. Hence, there is a need for clarification, to allow women to be adequately informed of the risk of use of these products, possibly preventing future harm.

This paper aims to review the literature and provide an overall risk estimate for the association between perineal talc use and ovarian carcinoma. We will also perform subgroup analyses by the method of talc application, the duration of talc use, the total number of perineal talc applications, and the type of ovarian cancer developed to further elucidate the relationship between talc use and ovarian carcinoma.

METHODS

Study Protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.¹⁴ R.P. performed a systematic search of the databases MEDLINE (from 1950), PubMed (from 1946), Embase (from 1949), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), LILACS, and the Cochrane Central Register of Controlled Trials through 22 August 2017 to identify relevant articles. The search used the terms ("talc" OR "talcum

powder") AND ("ovarian cancer" OR "ovarian carcinoma"), which were searched as text word and as exploded medical subject headings where possible. We also searched the reference lists of relevant articles for appropriate studies. No language restrictions were used in either the search or study selection. We did not search for unpublished literature.

Study Selection

We included studies that met the following inclusion criteria: (1) the study investigated the perineal use of talc in relation to risk of development of ovarian cancer; (2) the study reported adverse events as an odds ratio (OR), or the data were presented such that an OR could be calculated; (3) the 95% confidence interval (CI) was reported, or the data were presented such that the CI could be calculated; and (4) the study involved a minimum of 50 cases. We excluded studies that did not meet the inclusion criteria.

Data Extraction

One of us (R.P.) performed data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, population type, country, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs or data used to calculate CIs, and the type of ovarian cancer. R.P. assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS); however, no studies were excluded on the basis of NOS score.¹⁵ Authors were not contacted for missing data. Adjusted ratios were extracted in preference to nonadjusted ratios; however, where ratios were not provided, R.P. calculated unadjusted ORs and CIs.

Statistical Analysis

One of us (G.D.E.) calculated pooled ORs and 95% CIs for the effect of any perineal talc use with all ovarian cancers using a random effects model.¹⁶ Analyses were also performed based on the method of administration (diaphragm, sanitary napkins), duration of use, and type of ovarian cancer developed (all mucinous, mucinous invasive, mucinous borderline, all serous, serous invasive, serous borderline, endometrioid, clear cell). For long-term talc use, we extracted the odds ratio for the group with the longest duration of talc exposure compared with controls, provided that group used talc for a minimum duration of 10 years. For overall lifetime talc applications, groups within each study were divided into either <3600 lifetime applications, equivalent to less than approximately 10 years of daily use, or >3600 applications. Where a group from a study did not completely fit into this dichotomy, we placed it into the category it most closely fit. Details on the categorization of individual groups are available in eTable 1 (<http://links.lww.com/EDE/B261>). Odds ratios were pooled for invasive serous, invasive mucinous, borderline serous, and borderline mucinous tumors individually. However, as many studies reported only all mucinous or all serous in a single

group, we also ran analyses for risk associated with all mucinous and all serous tumors. Where a study reported separately as borderline and serous, both odds ratios were included separately in the meta-analysis, to ensure all available data were considered.

We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively.¹⁷ We quantified publication bias using the Egger's regression model,¹⁸ with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical nonsignificance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n + 10$, with n being the number of studies included in the meta-analysis.¹⁹ All analyses were performed with Comprehensive Meta-analysis (version 3.0; Biostat, Englewood, NJ; 2014).

RESULTS

Study Characteristics

We performed a broad literature search of electronic databases, identifying 363 citations for review (Figure 1). Initially, 318 studies were discarded, with many being narrative reviews, duplicates, animal studies, opinion pieces, editorials, or otherwise irrelevant. Forty-five citations were selected for full-text review. Of these, three were excluded due to being associated with endometrial rather than ovarian cancer, two were meta-analyses, five were duplications of data from the same study, one involved non-perineal application of talc, and seven were otherwise irrelevant. No studies were excluded for failing to report an odds ratio or for not providing the necessary raw data from which an odds ratio could be provided. Some studies provided only the raw data, i.e., the number of cases and controls with and without perineal talc use. This allowed an unadjusted odds ratio to be calculated, which was then included in the analysis. Overall, 27 studies were selected. Note that Wu et al³³ (2015) include results from Wu et al³⁶ (2009); however, only Wu et al³⁶ (2009) reported on non-perineal talc use, total lifetime applications, and long-term talc use. Hence data were extracted from Wu et al³³ (2015) for the "any perineal use" outcome, and from Wu et al³⁶ (2009) for the three other outcomes previously mentioned. Hence, while 27 studies were included in the analysis, only 26 were included in the any perineal use analysis. Three studies were cohort studies, including 890 cases and 181,860 person-years.^{12,13,20} The remaining 26 studies were case-control studies, with a total of 13,421 cases and 19,314 controls. The case-control studies are described in eTable 1 (<http://links.lww.com/EDE/B261>), while the cohort studies are described in eTable 2 (<http://links.lww.com/EDE/B261>).

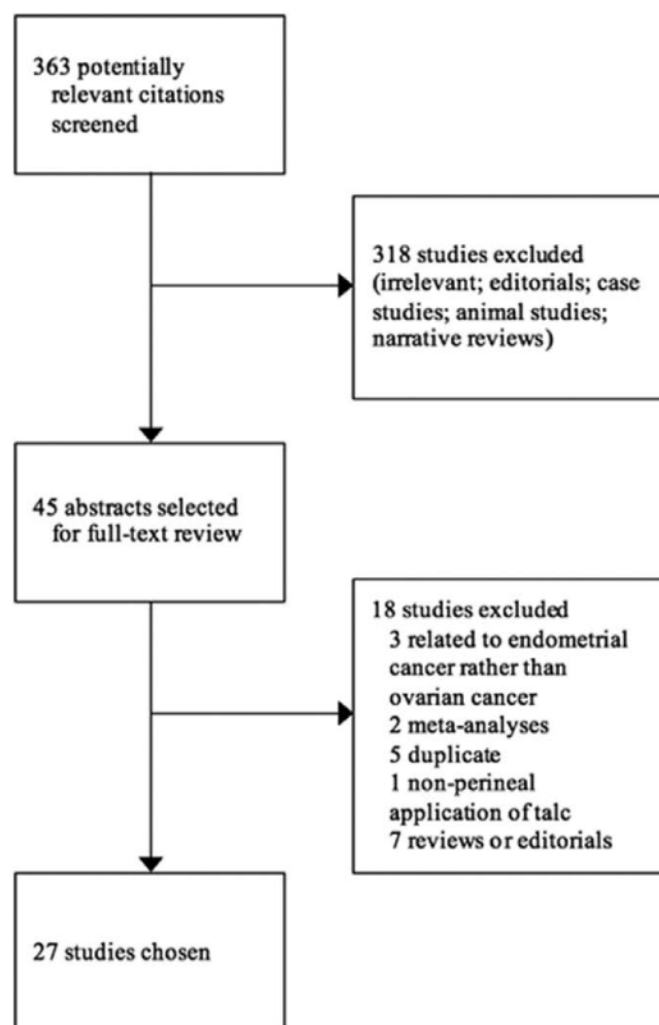


FIGURE 1. PRISMA flowchart for literature search and study selection.

[lww.com/EDE/B261](http://links.lww.com/EDE/B261)). In total, studies involving 14,311 cases of ovarian cancer were included in this review.

The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS), which involves separate assessment tools for both case-control and cohort studies.¹⁵ The highest score awarded was 8/10, and the lowest was 5/10. The mean score was 7.0. Almost all studies lost points because the exposure to talc was ascertained through self-report rather than an independently verified source, and because the interviewer was not blinded to cases and controls. Many studies also failed to specifically describe that their chosen controls did not have a personal history of previous ovarian cancer. It may be the case that this was done, but not reported in the study methods. Generally, case ascertainment and matching controls based on age and other factors, often geographical location or ethnicity, were well performed in the reviewed studies. The breakdown of individual study scores is included in Tables 1 and 2. Overall, the quality of studies included in

TABLE 1. Summary of Pooled Effect Sizes for Examined Outcome Variables

	No. Studies	Effect Size	Publication		
		OR (95% CI)	Heterogeneity		Bias
			<i>I</i> ²	<i>P</i>	<i>P</i>
Method of talc use					
Any perineal	26	1.31 (1.24, 1.39)	10.52	0.31	0.09
Any non-perineal	5	1.24 (1.01, 1.51)	66.84	0.02	0.86
Diaphragm	8	0.84 (0.68, 1.05)	14.76	0.31	0.64
Sanitary napkins	12	1.15 (0.94, 1.41)	43.82	0.05	0.17
Length of talc use					
Long-term use (>10 years)	12	1.25 (1.10, 1.43)	45.11	0.04	0.31
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0.20
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0.40
Type of ovarian cancer					
All serous	10	1.32 (1.22, 1.43)	0.00	0.75	0.44
Serous invasive	5	1.32 (1.13, 1.54)	25.10	0.25	0.75
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0.83
All mucinous	9	1.12 (0.94, 1.33)	5.79	0.39	0.79
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	NA ^a
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.22	0.96
Endometrioid	8	1.35 (1.14, 1.60)	0.00	0.61	0.78
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0.22

^aNA = not applicable; no publication bias ... result available when there are fewer than three studies in the analysis.

this review was reasonably high. No studies were excluded from the review based on NOS score.

All studies reported at least an odds ratio for any perineal use of talc and its association with ovarian cancer. As previously described, Wu et al³⁶ (2009) was not included in this analysis to prevent duplication of data. Five studies reported on only non-perineal exposure. Additionally, eight studies provided data for use of talc on a diaphragm, and 12 for sanitary napkins. Twelve studies provided an odds ratio for long-term talc use and its association with ovarian cancer; however, the chosen threshold for long term was variable, from more than 10 years to more than 37.4 years. Five studies reported on the total number of talc applications. It was frequently necessary to report different groups from a single study separately to perform the meta-analysis of this outcome, with the groupings being described specifically in eTable 1 (<http://links.lww.com/EDE/B261>). Ten studies reported odds ratios for all serous ovarian cancers, five reported for serous invasive cancers, and three reported for serous borderline cancers. Similarly, nine reported for all mucinous cancers, two for mucinous invasive, and three for mucinous borderline. Eight studies reported odds ratios for endometrioid ovarian cancer, and three reported for clear cell ovarian cancer.

Quantitative Data Synthesis

The results of the initial pooling of data from all studies are summarized in Table 1. Pooling of data revealed an increased risk of ovarian cancer associated with any perineal use of talc (Figure 2A; OR = 1.31; 95% CI = 1.24, 1.39). Use of talc long term (>10 years) was also associated with an increased ovarian cancer risk (Figure 2B; OR = 1.25; 95% CI = 1.10, 1.43). Both <3600 total lifetime applications (OR = 1.32; 95% CI = 1.15, 1.50) and >3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) of talc were associated with an increased risk of ovarian cancer, with a slightly higher risk in the group with greater usage. Talc use on diaphragms or on sanitary napkins was not individually associated with increased risk of ovarian cancer. Any perineal talc use was associated with any serous (Figure 2C; OR = 1.32; 95% CI = 1.22, 1.43), serous invasive (OR = 1.32; 95% CI = 1.13, 1.54), serous borderline (OR = 1.39; 95% CI = 1.09, 1.78), and endometrioid (Figure 2D; OR = 1.35; 95% CI = 1.14, 1.60) subtypes of ovarian cancer, but not the other subtypes.

We performed a subgroup analysis stratifying by study design. It is important to note that there were only three cohort studies, each of which did not report on all the assessed associations. For any perineal talc use, only case-control studies showed an association with ovarian cancer (Figure 2A; OR = 1.35; 95% CI = 1.27, 1.43), while no association was noted for cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). For the other associations assessed, the results are reported in Table 2. In cohort studies, the only association found was between perineal talc use and the incidence of serous invasive cancer subtypes (OR = 1.25; 95% CI = 1.01, 1.55). For borderline serous, borderline mucinous, invasive mucinous, and clear cell ovarian cancer subtypes, no cohort studies provided data for the association and hence the odds ratios reported in eTable 2 (<http://links.lww.com/EDE/B261>) are derived entirely from case-control studies. The only outcome reported in all three cohort studies was any perineal talc use; hence the available data from prospective studies were limited.

A subgroup analysis related to study population setting, i.e., in the hospital or in the general population, was performed for any perineal talc application. Generally, hospital-based studies were older (pre-2000) than the community-based studies. There were seven hospital-based studies, all of which were case-control studies. There were 20 population-based studies, including 17 case-control studies and all three cohort studies. There was no difference between the pooled results for hospital- and population-based studies (OR = 1.22 vs. 1.33), respectively.

There was heterogeneity in the analysis of non-perineal applications of talc ($I^2 = 66.84$; $P = 0.02$). There was no heterogeneity for any of the other outcome measures in either the meta-analysis of all available studies or the subgroup analyses. There was no publication bias in the meta-analysis of any genital talc exposure and ovarian cancer, which included all the studies in the review, except Wu et al³⁶ (2009) (Figure 3; $P = 0.09$). The result for publication bias for each of the individual analyses is included in Table 1.

TABLE 2. Summary of Pooled Effect Sizes in Subgroup Analysis by Study Design

	Case-Control Studies (n = 24)				Cohort Studies (n = 3)			
	No. Studies	Effect Size	Heterogeneity		No. Studies	Effect Size	Heterogeneity	
		OR (95% CI)	I ²	P		OR (95% CI)	I ²	P
Method of talc use								
Any perineal use	23	1.35 (1.27, 1.43)	0.00	0.77	3	1.06 (0.90, 1.25)	18.89	0.29
Non-perineal use	5	1.24 (1.01, 1.51)	66.84	0.02	0	NA	NA	NA
Diaphragm	7	0.81 (0.61, 1.08)	21.92	0.26	1	0.92 (0.68, 1.24)	0.00	1.00
Sanitary napkin	10	1.27 (0.98, 1.65)	40.49	0.09	2	0.93 (0.77, 1.13)	0.00	0.77
Length of talc use								
Long-term use	11	1.29 (1.13, 1.47)	40.53	0.08	1	0.98 (0.75, 1.29)	0.00	1.00
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0	NA	NA	NA
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0	NA	NA	NA
Type of ovarian cancer								
All serous	12	1.34 (1.23, 1.47)	0.00	0.71	2	1.19 (0.97, 1.47)	0.00	0.61
Serous invasive	3	1.36 (1.05, 1.75)	47.96	0.15	2	1.25 (1.01, 1.55)	0.00	0.33
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0	NA	NA	NA
All mucinous	9	1.15 (0.93, 1.41)	21.03	0.26	2	0.96 (0.61, 1.53)	0.00	0.84
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	0	NA	NA	NA
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.21	0	NA	NA	NA
Endometrioid	6	1.39 (1.16, 1.66)	0.00	0.52	2	1.09 (0.66, 1.80)	0.00	0.48
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0	NA	NA	NA

NA = not applicable; no cohort studies reported on the relevant associations.

DISCUSSION

The present meta-analysis reports a positive association between perineal talc use and ovarian cancer, specifically of the serous and endometrioid histologic subtypes. The mechanism by which perineal talc use may increase the risk of ovarian cancer is uncertain. It has been previously proposed that talc, as a foreign body, may ascend from the vagina through to the uterine tubes and instigate a chronic inflammatory response, which may predispose to the development of ovarian cancer. It is argued that cellular injury, oxidative stress, and local increase in inflammatory mediators such as cytokines and prostaglandins may be mutagenic and hence promote carcinogenesis.²¹ In support of this hypothesis, it has been found that hysterectomy or bilateral tubal ligation, in which ovarian exposure to inflammatory mediators would be significantly curtailed, is associated with a reduced risk of ovarian cancer.^{22–24} However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is not inversely associated with the incidence of ovarian cancer, as may be expected if the etiology was related to chronic inflammation.^{25,26} It has also been found that human epithelial ovarian cells have an unusually low expression of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which would reduce their sensitivity to the action of NSAIDs.²⁷ The potential mechanism by which genital talc is associated with an increased risk of ovarian cancer hence remains unclear.

An important finding of this study is that talc use appears to be associated with increased risk of serous ovarian

cancer, of both invasive and borderline types, and not with mucinous ovarian cancer. Additionally, endometrioid ovarian cancers but not clear cell cancers were significantly associated with perineal talc use. Intriguingly, a meta-analysis examining the effects of tubal ligation of ovarian cancer risk found a reduced risk of the same subtypes of ovarian cancer as mentioned here: serous and endometrioid, but not mucinous.²⁴ If chronic inflammation due to ascending foreign bodies is indeed the mechanism by which talc use is associated with increased ovarian cancer risk, then these results fit the picture. The results for non-perineal application of talc were still positive but of lower magnitude, supporting the hypothesis of ascending foreign bodies causing chronic inflammation. It is plausible that non-perineal application of talc may cause increased risk through, e.g., the respiratory tract. Unfortunately, the evidence remains insufficient to understand the mechanism with any reasonable certainty.

We also found a slightly greater increased risk of ovarian cancer with >3600 lifetime applications compared with those with <3600 lifetime applications. The number of lifetime applications is a more valid measure of the patient's exposure to perineal talc than either duration or frequency of use alone. This finding also supports the chronic inflammatory hypothesis, as repeated exposure would induce a longer period of chronic inflammation, and therefore should increase the predisposition to the development of ovarian cancer. It is notable that these data were only available from

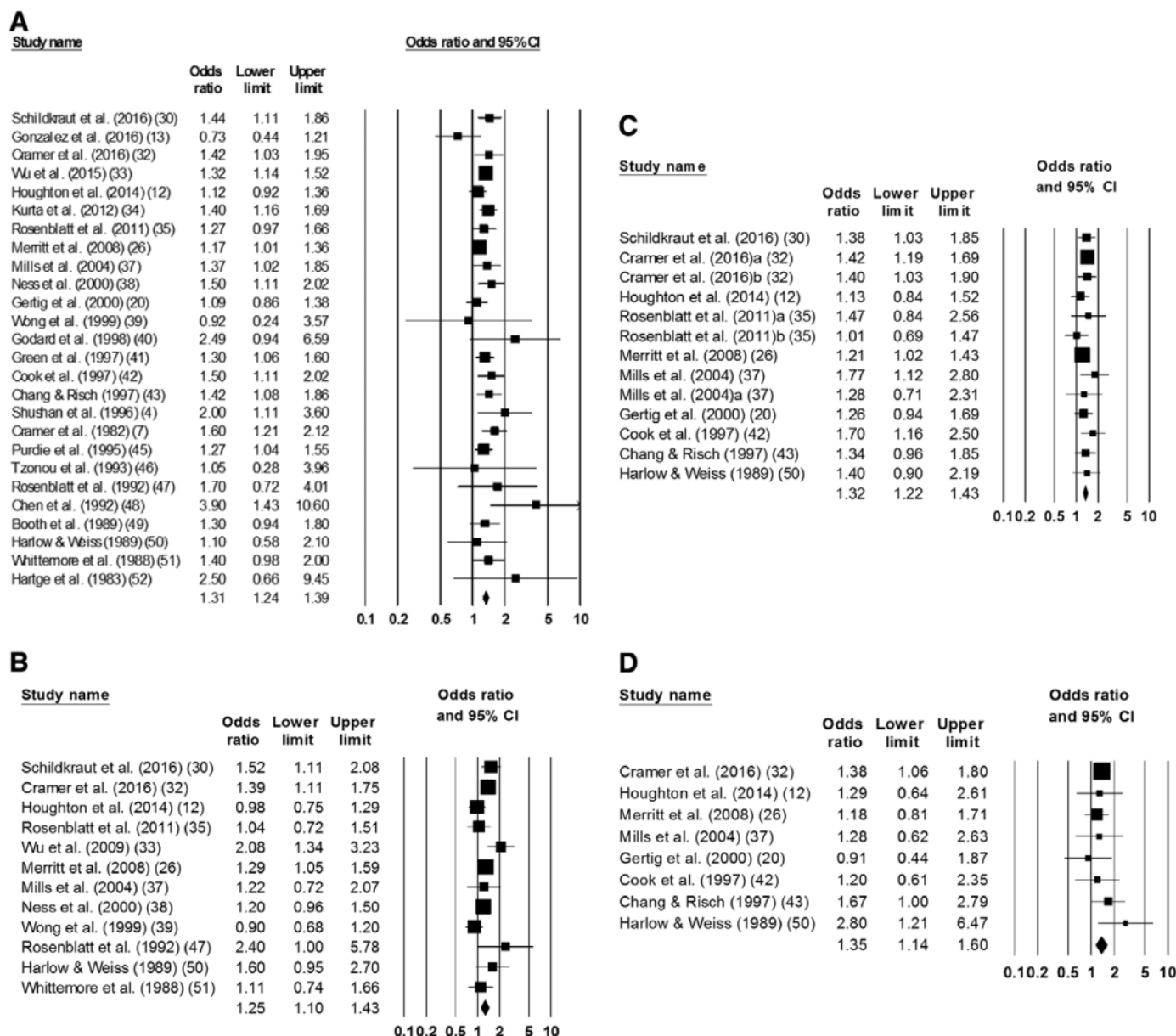


FIGURE 2. A, Any perineal talc use is associated with an increased risk of any ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). B, Long-term perineal talc use (>10 years use) is associated with an increased risk of any ovarian cancer, but of a lower magnitude than any perineal use (OR = 1.25; 95% CI = 1.10, 1.43). C, Any perineal talc use is associated with an increased risk of serous ovarian cancers (OR = 1.32; 95% CI = 1.22, 1.43). D, Any perineal talc use is associated with an increased risk of endometrioid type ovarian cancers (OR = 1.35; 95% CI = 1.14, 1.60).

case-control studies, as the three cohort studies did not sufficiently record duration and frequency of use to be included in the analysis. This retrospective finding is therefore prone to recall bias.

This meta-analysis had several strengths. None of the analyses in this review had statistically significant heterogeneity, except for non-perineal application, which indicates consistency in the direction and magnitude of the effect size between individual studies, and strengthening the reliability of the pooled effect sizes. Another strength of this review is

the large number of overall cases ($n = 14,311$), improving the power of the meta-analysis to detect a relatively small effect size, as occurred in this case. Another strength of this review is that the included studies were of relatively high quality as assessed through the NOS, reducing the potential for bias in the conclusions drawn. The NOS revealed that the most common limitations of the included case-control studies were the failure to blind interviewers to case-control status of subjects in the interview, and reliance on memory and self-report for collection of data on perineal talc use.

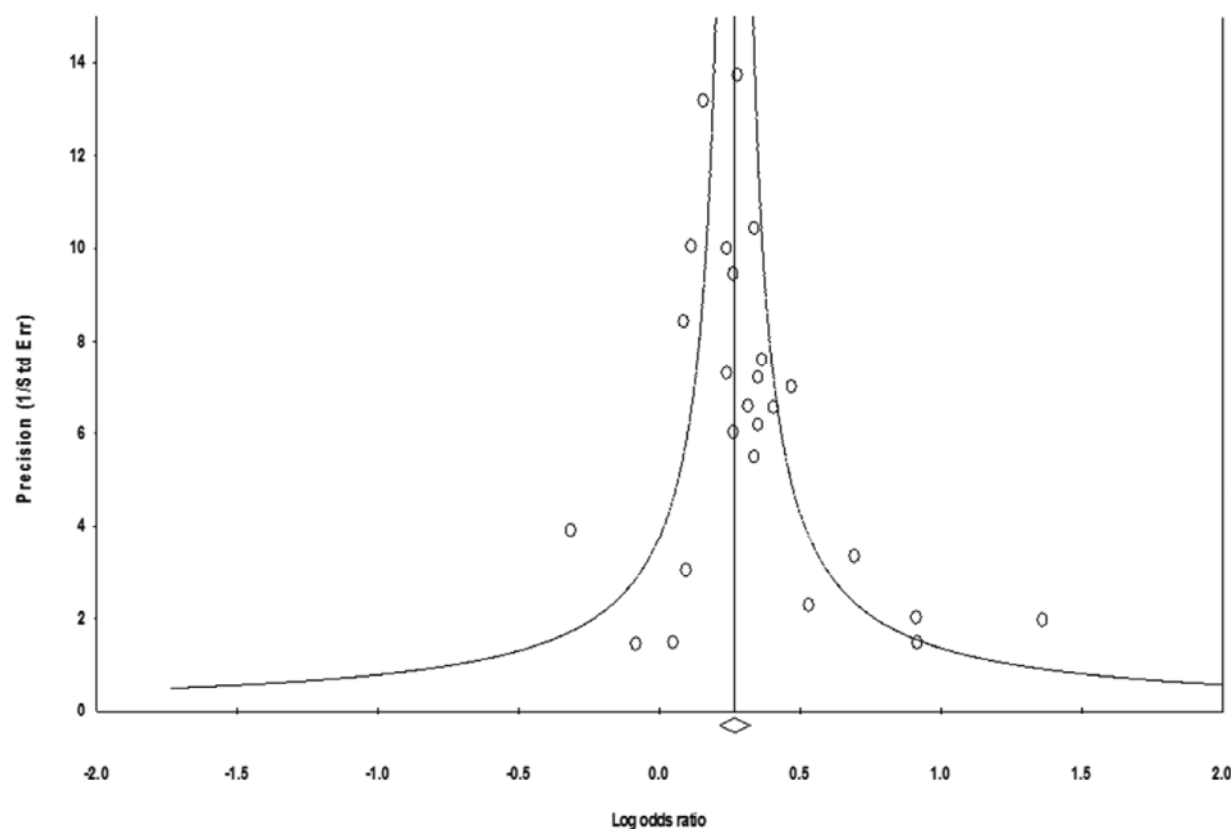


FIGURE 3. Funnel plot for the meta-analysis of studies examining any perineal talc use and risk of ovarian cancer ($P = 0.09$).

A limitation of this study is that it pools nonrandomized studies, primarily case-control studies. The retrospective nature of case-control studies introduces the potential for recall bias. In this case, it is entirely possible that patients with ovarian cancer may be more aware of their previous talc use and hence be more likely to report higher past use. It is possible to attempt to overcome this by blinding the participants to the nature of the study, usually by asking spurious questions; however, the effectiveness of this approach may be limited.²⁸ Many of the studies in this review recorded data about talc use as part of a more extensive questionnaire focused on other associations, which may reduce the potential for recall bias. However, since the initiation of lawsuits in 2014, there has been extensive media coverage regarding this association, and the potential for recall bias in case-control studies conducted since then may be exacerbated.

Cohort studies are useful in that they are prospective; however, the low incidence of ovarian cancer results in relatively small number of cases even in large cohorts, as seen in the three cohort studies included in this review.²⁹ Considering potential exposure misclassification issues in case-control studies, the effect for any perineal talc use was very weak in a small number of cohort studies. However, an association between talc use and serous invasive ovarian cancer was found.

Of the studies in this review, case-control studies achieved much large number of cases, in some instances in excess of 2000 cases and a similar number of age-matched

controls, which provide greater statistical power for the detection of an effect size of small magnitude. Hence while case-control studies are low-level evidence, they have been preferred in the investigation of the association between talc use and ovarian cancer. They also have the important advantage of not requiring 15 or more years of follow-up, as is necessary for a cohort study to sufficient detect cases of ovarian cancer relative to certain exposures. One potential way to overcome this limitation in future studies is to ensure that talc use is always included in questionnaires of any cohort studies investigating ovarian cancer. It is important not only that talc use be investigated but also the precise location, duration, and frequency of use. As it stands, a meta-analysis of observational studies such as the present study provides the highest level of evidence practically feasible for this research question.

CONCLUSIONS

The results of this review indicate that perineal talc use is associated with a 24%–39% increased risk of ovarian cancer. While the results of case-control studies are prone to recall bias, especially with intense media attention following the commencement of litigation in 2014, the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association. Additional epidemiologic evidence from prospective

studies with attention to effects within ovarian cancer subtype is warranted. There is a substantial need for further research on a potential mechanism by which ovarian cancer may be caused by talc, as this will allow a causal relationship to be established or rejected with more certainty. However, particularly because of the dearth of screening tests available for this high-mortality cancer, it is important that research into this association continue as it is a potential avenue for cancer prevention.

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Exhibit 55

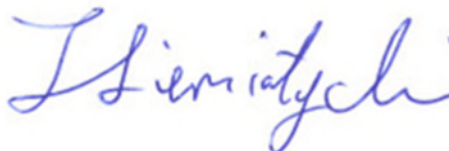
**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
JACK SIEMIATYCKI MSc, PhD**



Date: November 16, 2018

Jack Siemiatycki MSc, PhD

EXPERT REPORT OF JACK SIEMIATYCKI MSc, PhD
On
TALCUM POWDER USE AND OVARIAN CANCER

Jack Siemiatycki, MSc, PhD, FCAHS

106 Columbia Avenue

Westmount, Quebec, Canada

November 16, 2018

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1. My mandate

I have been retained to assess the epidemiologic evidence regarding the **general causation** between perineal (or genital) use of talcum powder products and risk of ovarian cancer. The question is: "Can application of talcum powder products in the perineal region cause ovarian cancer?"

All of my opinions in this report are stated to a reasonable degree of scientific certainty.

2. My credentials, expertise and experience

I am a tenured Professor of epidemiology at the University of Montreal and an Adjunct Professor of epidemiology at McGill University in Montreal. I have received prestigious national research awards in Canada, such as National Health Scientist Salary Award, Medical Research Council Distinguished Scientist Award, Canada Research Chair in Environment and Cancer and, currently, I hold the Guzzo-Cancer Research Society Chair in Environment and Cancer. I am an elected fellow of the Canadian Academy of Health Sciences. I was awarded a lifetime achievement award by the Canadian Society for Epidemiology and Biostatistics, the premier professional organisation in our discipline.

Trained in statistics and in epidemiology, I have devoted most of my research career to investigating links between environmental, occupational and lifestyle factors and various types of cancer. My research has been both substantive – namely, looking at particular factors and their possible relationship to particular cancers - and methodological – namely, exploring how to evaluate and enhance the validity of epidemiologic research through various prisms: study design, data collection methods and statistical analysis. Of my approximately 250 research publications, about one quarter would be considered to have methodological focus.

I have held various leadership positions, including the elected presidency of the Canadian Society for Epidemiology and Biostatistics, and elected membership on the Board of the American College of Epidemiology. I have been invited to serve on over 160 Boards, Scientific Councils and Expert Panels for a host of governments, universities or research agencies. Examples include: Board of Directors of the Canadian National Cancer Institute, member of expert panel tasked with recommending priorities for action under the

Canadian Environmental Protection Act, member of external peer review panel of the Epidemiology branch of the US National Cancer Institute (NCI), member of two different expert advisory bodies to research projects at the NCI, consulted by President Clinton's Cancer panel, member of external peer review panel for the Helmholtz German national medical research agency, Chair of the Scientific Council of the largest prospective study of causes of cancer being conducted in France, and others of that nature.

I have been associate editor of the American Journal of Epidemiology and the International Journal of Environmental Health. In addition, I have served as reviewer for about 20 journals. I have served as a chair and as a member of grant review panels for major Canadian scientific funding agencies.

My research programme has been well funded by Canadian funding agencies for over 35 years. I have conducted research and published on the carcinogenicity of a large number of agents in the occupational environment (e.g. asbestos, silica, welding fumes) and in the general environment (e.g. smoke from wood stoves, urban air pollution) and lifestyle factors (e.g. smoking, alcohol, use of cell phones).

I have taught and supervised epidemiology students and many of my former trainees are now faculty members in universities around the world.

I have had a long association with the International Agency for Research on Cancer (IARC). IARC is the premier institution in the world for cancer epidemiology and for environment and cancer research. It has several mandates, including the organisation and compilation of standardised high quality data on cancer incidence around the world, the conduct of original research, and the evaluation of the carcinogenicity of different agents with which humans come into contact. The latter is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens. Since the inception of this program in 1971, there have been about 120 meetings held and approximately 1100 agents have been evaluated.

A particular point of pride for me is that over the years, research results from my team have been cited as part of the information base on 69 of the 1100 agents that have been evaluated, probably making my team the most cited epidemiology team in the history of the IARC Monograph program.

My association with IARC began when I did a post-doctoral fellowship there in 1977-79. Over the intervening years I have collaborated with scientists at IARC on various research projects. I was a member of the 18-member Scientific Council of IARC from 2006 to 2010 including two years as elected Chairman of the Council. The Scientific Council oversees all of the scientific activities at IARC; its members are named by the member states of IARC. I have been invited to sit on IARC Monograph international expert panels for 5 of the 60 panels convened in the past 25 years. One of the IARC Monograph panels of which I was a member was tasked with evaluating: "Carbon black, titanium dioxide and non-asbestiform talc." Out of the 16 invited experts who participated in the meeting as members of the Working Group, I was selected to chair the meeting.

Subsequent to the IARC meeting and the report of the meeting, a small subgroup of members of the IARC Working Group, of which I was a member, conducted and published a meta-analysis of the results of the studies that had been available to the IARC Working Group (Langseth, 2008)

Although I have not personally produced original data collection studies on the topic, I am well qualified to review the epidemiologic evidence. I have participated in two published reviews of the issue. The methodologic expertise and analytical skills required to critically review and evaluate such evidence is generic to the vast area of environmental epidemiology of cancer. I am routinely asked by journals and grant agencies to provide expert opinions on topics for which I have not produced original data collection studies, but that are within the purview of my expertise. The invitation by IARC to chair the meeting at which talc was evaluated is testimony to the fact that my competence and expertise in this matter are internationally recognized by peers. I do not claim expertise in various adjoining domains that inform this issue, including physiology, pathology, clinical oncology, experimental toxicology, geology and mineral chemistry. However, I do have the

expertise and skill to assimilate information that is provided by experts in these areas. I have previously submitted a report on my review of the evidence regarding talcum powder products and ovarian cancer in October 2016.

I have previously served as an expert witness for plaintiffs in one U.S. court case, and that was a talc litigation in Los Angeles in 2017. (Eva Echeverria, BC628228, Johnson and Johnson Talcum Powder Cases, CA JCCP No. 4872), and I testified that the genital use of talcum powder products can cause ovarian cancer.

I have served as an expert witness in two Canadian court cases, neither having to do with talc or hygiene powders or ovarian cancer. One case dealt with a class action lawsuit on behalf of a town in Canada adjoining a Canadian military base where there had allegedly been a spill of trichloroethylene that seeped into the water table of the town. The residents claimed that the contamination had caused cases of cancer. I was an expert for the defence, the Canadian government, and I testified in 2012. (Province of Quebec Superior Court file 200-06-000038-037).

The other case was a class action on behalf of Quebec residents who contracted cancer and had been smokers, claiming that the tobacco companies were responsible for their diseases. I was an expert for the plaintiffs and I testified in 2014. (Province of Quebec Superior Court file 500-06-000076-980).

In my work as an expert for legal cases, my time is billed at the rate of \$450 per hour for research, report preparation, communications with counsel, participation in depositions, and testimony in court.

3. Overview of my methodology

The basis of my opinions derive from my education, training, experience, research and what is accepted within the community of leading scientists practicing in the field of epidemiology. My opinions are based on my review of the relevant materials, published in the scientific literature and/or produced in this case; including internal company documents, as well as relevant depositions, reports and testimony in the talcum powder product litigation. To reach my conclusions, I have employed the same scientific

methodology and rigor that I use in my research, in my publications and in the consulting and advising that I carry out on behalf of governments, public health agencies and research institutes. This includes a review of the relevant published literature, expert judgment to assess the quality and meaning of the various studies that were reviewed, and syntheses of the available evidence and any other pertinent medical and scientific evidence of which I am aware. The methods I used to derive and present my opinions are those used in general in the assessment of causal relations in medicine and public health, and more specifically in epidemiology. The methods are based on the experience and insight I have accumulated over 40 years of research, consulting, reviewing and student supervision, from discussions and interactions with leading epidemiologists, service on multiple IARC panels, and from reading evolving ideas in the scientific literature, including such seminal works as Bradford Hill's (Hill 1965) writings on assessing causality.

My opinions may be further supplemented and refined, subject to results that may come from further medical and scientific study and research and the continued review of additional information and discovery materials produced in this litigation.

4. The science of epidemiology

This section is designed to provide a non-specialist reader with information and definitions about epidemiology and biostatistics that are needed to understand the basis of my evaluation on talcum powder products and ovarian cancer. I do not present in this section the actual data and evidence regarding talcum powder products and ovarian cancer.

Epidemiology is the science of occurrence of diseases in human populations. It is concerned with the patterns of disease occurrence and also with identifying the factors that influence disease occurrence. These two sets of concerns are sometimes referred to respectively as descriptive epidemiology and analytic epidemiology. The first addresses such issues as the incidence of the disease in different geographic areas, in different time periods, or at different ages and sexes. The second addresses more focused questions on the specific environmental and/or lifestyle and/or genetic factors that might influence the incidence of disease.

The word “epidemiology” has the same etymologic roots as the word “epidemic”, which signifies that, initially, epidemiology grew out of the study of epidemics. Such epidemics were often of a microbial origin (e.g. viruses, bacteria, parasites). But increasingly in the 19th and especially in the 20th century, it became clear that the etiology (i.e. causation) of chronic diseases such as cancer could also be elucidated by studying their patterns of occurrence.

While there were many studies carried out in the early to mid-20th century that we would now qualify as epidemiological in nature, the discipline of epidemiology and its methods started to become formalized in the 1950’s and 1960’s. There are now departments of epidemiology in most large universities that have health science research and teaching activities and there are many national and international societies of epidemiology.

Epidemiology is characterized by its mainly observational and non-experimental approaches. It is a discipline that is not primarily based in the laboratory; rather it is based in society. That is the source of its strength, and its weakness. Because it deals with people in the reality of their lives, it is the most pertinent approach to understanding the links between people’s lifestyles and environments and their health and disease. However, because it is based in society, it by necessity confronts the extreme complexity of human lifestyles, environments and diseases. And because we cannot experiment with people’s lives, we cannot control the conditions in which people are exposed. The methods of epidemiologic research are complex and differ from study to study. Statistical methods play an important role in trying to tease out the role of different variables and in determining whether the observed results may be attributable to chance, to bias or to real effects of putative risk factors. It is usually necessary to assemble evidence from several data-collection studies on a given topic before being able to draw inferences about causality.

4.1 Some basic measures and notions used in epidemiology

In this section I will review a number of concepts that need to be understood in order to properly understand my review of the evidence regarding talc powder and ovarian cancer. It is intended for readers who may not be expert in epidemiology. In this section I will not necessarily tie the concepts and definitions to the talc-ovarian cancer issue; that part will

be left for later. For now, I am simply introducing the non-epidemiologist reader to terminology and concepts with which she/he may not be very familiar.

Prevalence of disease. The prevalence of a disease refers to the proportion of a population who are living with the disease at any given point in time.

Incidence of disease. The incidence of a disease refers to the proportion of a population who are newly diagnosed with the disease during a certain period of time. The bridge between incidence rate and prevalence rate is the average duration of the disease, or how long people live with it before they are cured or pass away. In fact, while incidence and prevalence are foundational concepts in epidemiology, it is only incidence that figures prominently in the evaluation of carcinogenicity of talc.

Risk of disease. The risk of disease is a term that can refer to incidence or prevalence. The meaning should be clear from the context in which it is used. For studies of cancer, it almost always refers to incidence of disease. This is the way I will use the term in this report.

“Cause” of disease. A cause of a disease is any agent or characteristic (environmental, lifestyle or genetic) that increases the probability of getting the disease or it may simply advance or hasten the onset of the disease. It may act alone or it may act in concert with other factors over a lifetime to cause the disease. It may act immediately (e.g., cyanide as a cause of poisoning; lack of seat belt use as a cause of car accident mortality) or it may take many years for the effect to become manifest (e.g., lack of physical activity as a cause of obesity). There may be many different causes for the same disease. (See explanation of Multifactorial Etiology below.)

Risk factor. As defined in the Dictionary of Epidemiology (Last 2001), a risk factor is an aspect of personal behavior or life-style, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with a health-related condition. The term *risk factor* is used rather loosely and depending on the context it can refer to a factor that directly causes a disease or a factor that is a strong marker for the proximal cause of the disease. As it is often used, I will

mainly use the term “risk factor” as a synonym for the noun “cause” of the disease. (eg. “Smoking is a risk factor for lung cancer.”)

Association. As defined in the Dictionary of Epidemiology (Last 2001), association refers to the degree of statistical dependence between two or more events or variables. Events are said to be associated when they occur more frequently together than one would expect by chance. Association does not necessarily imply a causal relationship.

Risk among unexposed (R_u) refers to the risk of disease among persons who are not (or were not) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have never* used talc in the perineal region.

Risk among exposed (R_e) refers to the risk of disease among persons who are (or were) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have* used talc in the perineal region.

Relative Risk: $RR = R_e/R_u$ = Risk among exposed/Risk among unexposed

When $RR > 1.0$, it indicates that exposure to the agent increases the risk of developing the disease. When $RR < 1.0$, it indicates that exposure to the agent prevents the disease.

When $RR = 1.0$, it indicates that the exposure to the agent has no bearing on the risk of getting the disease.

95% Confidence interval (95% CI). This refers to the precision of an estimate of a parameter. When we estimate the 95% CI for the RR, we are approximately saying that we are 95% certain that the true parameter underlying the study is within these limits. (The true interpretation is more subtle.)

Statistical significance of an association: Statistical significance is a measure of the departure of a set of data from some null hypothesis. Most commonly in epidemiology, the null hypothesis would state that there is no association between a factor and a disease. The null hypothesis can be operationalized in different ways, such as that the $RR = 1.0$, or that there is no trend between the degree of exposure and the RR. Once a study is conducted, the results can be compared with the expected results based on the null hypothesis, and the discrepancy from the null hypothesis is measurable with probabilities. This is done

either by computing a p-value or a confidence interval. If the p-value is very small or the confidence interval does not include the null value, then we say that an observed association between the putative risk factor and the disease is unlikely to be due to chance alone.

It is important to note that while statistical significance is a tool for assessing whether an observed association is attributable to chance alone, it is not a very effective tool for establishing the absence of an association. That is, the absence of statistical significance is not tantamount to proof of the absence of an association. The absence of statistical significance can be due to the true absence of an association, but it can also be due to the study not having sufficient statistical power or to bias or confounding in the research methods. Furthermore, it should be noted that the conventional dichotomization of results as “statistically significant” or not, based on a particular cutpoint on the p-value scale (eg. $p = 0.05$), is a gross simplification. The compatibility of the data with the null hypothesis of no association is in truth on a continuous scale and the dichotomization is arbitrary and potentially misleading, especially when the observed p-value is close to the arbitrary cutpoint.

In practice, epidemiologists have been moving away from using and reporting p-values and statistical significance, as it has become clear that the main contribution of an individual study is to provide an estimate of the relative risk and its range of plausible values, embodied in a confidence interval.

Cohort studies and case-control studies: Epidemiologic research projects can take many different forms. The two most common types of analytic epidemiologic studies are cohort studies and case-control studies. (Rothman, Greenland, & Lash 2008)

In a cohort study, it is typical to enrol a large number of subjects, determine which ones are or have been exposed to the factor of interest (e.g., talc) and follow them for some period of time to evaluate whether those who were exposed subsequently experienced different disease rates from those who were not exposed.

In a case-control study, by contrast, we start with people who have the disease under study (e.g. ovarian cancer) and a set of controls who do not have the disease, and we collect data

to determine whether the cases and the controls had different histories of exposure to the factor under study (e.g. talc).

It may be said that a cohort study proceeds from the cause to the effect, whereas a case-control study starts from the effect and backtracks to the cause. There are many variants on these basic designs. These descriptions of these types of study are somewhat simplified.

It is sometimes claimed that a prospective cohort design produces more valid and reliable RR estimates than a case-control study. But this is incorrect as a generalization. The validity and reliability are not determined by the overall architecture of the study, but rather by the specifics of the study, including how the study subjects were assembled, the nature of the variables under study (exposure, disease, confounders), exactly how the information was collected, the statistical power, and so on. There may be many reasons why a particular case-control study is more valid than a particular cohort study.

Relative Risk (RR) and Odds Ratio (OR). The cohort study design leads naturally to the estimation of risk of disease among exposed, and risk of disease among unexposed, and then to the ratio of those two, which is the RR. In case-control studies, because of the way the study samples are selected, it is impossible to estimate the risk of disease or the ratio of the two risks, R_e/R_u . However, under certain conditions which are well met in studies of cancer, it is possible to estimate an approximation of the RR. This is called the odds ratio, referred to as OR. In the rest of this report, I will consider evidence obtained from both cohort studies and case-control studies, and I will refer to the findings of these studies as RRs, even if technically speaking, the results from case-control studies are ORs.

Bias, confounding, effect modification. The aim in an epidemiologic investigation of a putative risk factor is to derive an accurate estimate of the RR between exposure to the agent and the disease at issue. Because the investigator does not control the conditions in which people live and are exposed to different agents and their willingness to participate in research, there are many potential sources of distortion in epidemiologic research. While there are many sources of distortion, they can be bundled into a few large families of sources of distortion.

Bias refers to a systematic distortion in study findings, resulting from the way the study was designed or the way the data are collected. Specific examples of types of bias will be discussed below as they pertain to talc and ovarian cancer.

Confounding is sometimes considered to be a type of bias, and sometimes it is considered a type of distortion on its own. This is merely a semantic distinction. Confounding refers to the situation where the association under study between factor F and disease D is distorted because there is a third factor X which happens to be correlated with F and which is a cause of disease D. For instance if we want to study the association between occupational exposure to talc in mines (factor F) and lung cancer (disease D), we need to be mindful of whether cigarette smoking (factor X) is more common in talc miners than in the rest of the population. Confounding differs from other types of bias in that it depends on relationships among different variables in the population, rather than characteristics of the study design and data collection.

Effect modification refers to the phenomenon whereby a given factor has a different effect in one sub-population than in another. If we study the association between that factor and the disease in the entire population without distinguishing the two sub-populations, we might end up with an estimate of the association that does not convey accurately the association in either sub-population. For instance, if it were the case that a certain genetic characteristic G increases the risk of pre-menopausal ovarian cancer but has no impact on post-menopausal ovarian cancer, then a study of the association between G and ovarian cancer that does not discriminate by menopausal status, would find an RR result somewhere between the null value among post-menopausal women and the true RR value among pre-menopausal women. Depending on the proportions of pre- and post-menopausal women in the sample, the overall RR might be so close to the null, that we might erroneously conclude that there is no association at all. In this example, it might actually be quite simple to detect the effect modification, since age is always recorded and menopausal status is usually recorded and investigators are sensitized to the possible effect modification of female cancers by hormonal status. Other potential effect modifiers may not be so easily available and they might not be on the radar screens of investigators. Effect modification can in some unusual circumstances completely wipe out a true causal

association (as when the agent causes cancer in some people but prevents cancer in others!). But generally, if there is a causal effect of the agent in one stratum of the population and no association in another stratum, and if we fail to stratify the population according to the effect modifier, it will have the effect of producing an overall RR that is lower than it truly is in the sensitive stratum and higher than it truly is in the insensitive stratum.

Effect modification is closely related to and sometimes synonymous with interaction or synergism.

Publication bias refers to the tendency for some evidence never to “see the light of day”. Namely, when results are “negative” or “null”, it may be that investigators never bother to submit them for publication, or alternatively that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small.

In this section I have briefly outlined some potential sources of distortion of a typical epidemiologic study. I have done this in a high-level generic way. Below, after presenting results of my review of pertinent literature on powders and ovarian cancer I will return to commenting on the possible impact of such distortions in this body of literature.

Exposure variable and exposure metric

An ***exposure variable*** can be anything that can influence the occurrence or outcome of disease. The term is used for such disparate entities as external components of what we eat, drink, breathe, hear or see and microbiological organisms, chemicals or forms of radiation.

Depending on the nature of the variable, information on an exposure variable can often be ascertained from epidemiologic study participants by questioning them. This is the case for variables like cigarette smoking or use of talc powders. For some variables, like exposure to a virus or to specific air pollutants or occupational chemicals, it is usually necessary to invoke more intensive data collection methods to ascertain exposure.

An ***exposure metric*** signifies a way of defining a variable for statistical analysis. The simplest metric is a binary variable: exposed or unexposed. For most exposure variables, like exposure to talc powder, there can be a very wide range of degree of exposure. And it is pertinent to create more nuanced exposure metrics that take into account the degree of exposure that different people have experienced, metrics such as duration of exposure, intensity or frequency of exposure and even cumulative measures of exposure over long periods of time.

Measurement error. Whenever we are measuring a variable in an epidemiologic study, be it smoking, or weight, or socio-economic status, or blood pressure, or any other variable, it is virtually inevitable that there will be some degree of error in the measurement. There are ways of collecting data that make them more or less likely to involve error, but it is almost impossible to ensure that variables are measured with perfect validity and precision. Even such a variable as the diagnosis of ovarian cancer is subject to differences of opinion among pathologists and oncologists and the presence or absence and the histologic type of tumour is not a guaranteed 100% perfect diagnosis. The ascertainment of the lifetime history of talc exposure by means of an interview with a woman in middle age or later in life is certainly susceptible to the caprices of memory and the way the questions are formulated may influence the validity of respondents' reports of lifetime exposure patterns. It is likely that habits that were performed regularly are more reliably recalled than activities that were sporadic or that only occurred many decades earlier. Similar issues arise for all other variables collected in such studies. We refer to measurement error as random (or non-differential) if the degree of measurement error does not differ between cases and controls in case-control studies or between exposed and unexposed in cohort studies. As a general rule of thumb, it can be asserted that random (or non-differential) measurement error has a predictable distorting effect on the RR. Namely, while there are some rather obscure exceptions, non-differential measurement error tends to attenuate the RR towards the null value of 1.0, and the more measurement error, the greater the attenuation. A full explanation for why this is so is quite technical and can be found in advanced epidemiology textbooks, such as Rothman, Greenland and Lash 2008. A very simple explanation is that the presence of measurement error in assigning exposed vs

unexposed status leads to dilution of both the exposed group and the unexposed group. That is, the ostensible exposed group (i.e. the folks who will be labelled as exposed based on the study data collection) will contain some folks who are truly unexposed and the ostensible unexposed group will contain some folks who are truly exposed. If there really is a difference in risk between the true exposed group and the true unexposed group, this difference will be watered down by the inadvertent inclusion in each group of folks who are really in the opposite group. An analogy is the cross-contamination of two cans of paint. Suppose we have a can of pure white paint and a can of pure red paint. Suppose we have a way of quantifying the difference in color tone between the two paints. Then suppose we take some spoonfuls from the red can and pour them into the white can, and likewise take a few spoonfuls of the white paint and pour them into the red can. Now the color contrast between the two cans has been attenuated. The color contrast in this example is like the relative risk in an epidemiological study which has been attenuated because the exposed and unexposed groups have been cross-contaminated.

Dose-response. It is important not only to assess whether there is an association between a variable and a disease when the variable is defined in a binary (exposed vs unexposed) way, but also when the variable is defined in a quantitative or semi-quantitative way. When we analyse the risk as a function of the degree or duration or intensity of exposure, we refer to this as a dose-response (or exposure-response) analysis. The example of the smoking and lung cancer is instructive about the value of different metrics, though it cannot be assumed that all risk factors act the same way. Studies using the binary metric for smoking (smoker/non-smoker) have been very consistent and persuasive in demonstrating an association between smoking and lung cancer. Further, when data are collected and analysed regarding the degree of smoking, it becomes clear that there is a monotonic dose-response relationship. That is, the more smoking, the higher the risk. And the quantitative metric that manifests the strongest association with lung cancer is the cumulative amount smoked over the lifetime. This is perfectly logical. Since the cumulative exposure metric embodies information on duration and on intensity, it can hardly be less predictive of risk than either of the dimensions alone.

We cannot assume that there is a universal form of a dose-response relationship for every true causal relationship. Most commonly, in toxicology and epidemiology, the relationship between exposure and risk is monotonic; that is, as one increases, so does the other. This can include linear relationships (i.e. where a straight line on a graph describes the relationship) or exponential or many other curvilinear forms. It is also possible that there may be a threshold effect (the risk only becomes apparent after a certain level of effective exposure) or some other non-standard relationship.

Both the qualitative metrics (ever/never) and quantitative metrics (a lot of use compared with a little use) are valid and useful metrics.

Sample size refers to the number of participants in the study. As a generalization, large studies produce more statistically stable and precise estimates than small studies. In fact the stability of estimates or precision of estimates is not a simple function of the number of participants, or subjects, in a study. The precision of estimates depends, among other things, on the type of epidemiologic design.

In a case-control study the main determinants are the numbers of cases and controls and the prevalence of exposure in the two groups; in a cohort study the main determinants are the numbers of participants, prevalence of exposure, and the incidence of the disease of interest over the period of follow-up in the exposed and unexposed groups.

There is sometimes confusion about the notion of sample size when we compare cohort studies with case-control studies. The operational aspect of an epidemiologic study of cancer that most influences the precision of an estimate of RR is not the total number of participants; rather, it is the smaller number between the number of exposed cases of disease and the number of unexposed cases. In a typical prospective cohort study, one might need to enroll 100,000 participants in order to end up with a certain number of cases (say, 500 cases) of the disease of interest (e.g. ovarian cancer). In a case-control design we might only need to enroll around 500 cases and 1500 controls to achieve the same statistical power as would be achieved by a cohort study of 100,000. The formal justification for this assertion is quite mathematical, and has to do with the fact that a sample of a population can give very accurate estimates of the characteristics of an entire

population. Thus, the simple comparison of 100,000 participants in a cohort study and 2,000 participants in a case-control study is in no way a valid marker for the relative statistical power of the two hypothetical studies. There are admittedly other advantages and disadvantages of the cohort vs the case-control design, and reviewers should consider the various aspects before deciding on the relative weight to give to the results of the different studies. But it is definitely not appropriate to merely compare the numbers of participants as an indicator of study validity.

While precision is based on multiple factors and different ones in case-control and cohort studies, there is a parameter which embodies the different factors quite well, and which is common to both case-control and cohort studies, namely, the number of exposed cases. For this reason, in laying out the various study results below, in addition to the relative risk estimates and their confidence intervals, I will show the numbers of exposed cases.

While it may affect the precision of estimates of RR, the size of the study does not in itself systematically affect the estimates of RR. That is, it is not the case that small studies produce systematically exaggerated RR estimates or systematically low RR estimates. However small studies can produce more wildly divergent RR estimates than large ones, in either direction, towards the null or away from the null.

Meta-analysis and pooled analysis: There are two distinct ways that evidence from multiple studies can be combined to derive a new overall statistical summary or synthesis of those studies, a meta-analysis and a pooled analysis. A meta-analysis uses the published results from each study and averages those results using some optimal weighting procedures. In order to implement a meta-analysis it is necessary to find all relevant studies on a topic that have published results in a fairly standardized way. The statistical algorithms typically used to average the results from different studies also provide statistics that evaluate how heterogeneous are the results from the different studies. The interpretation of such heterogeneity statistics is not straightforward. If the results from different studies are homogeneous, it adds to the confidence in the meta-estimate. If they are heterogeneous, it may indicate that the association is really different in different populations, or that there are some methodological characteristics of the different studies

that have influenced the results in different ways. Unless a significant methodological flaw can be identified that has caused the heterogeneity, the best overall estimate remains the meta-estimate.

A pooled analysis is one in which the investigator gets access not only to the published results from different studies, but rather to the individual data of every person in the studies. The latter is harder to achieve because it requires high buy-in and input from the investigators of the original studies; a meta-analysis is much easier to organise. Because a pooled analysis allows for standardization in the definition of variables and statistical models, it can be a more powerful means of summarizing data than the original studies themselves.

Multifactorial etiology of disease. Chronic diseases such as cancer are multifactorial in two distinct ways. On the one hand, each case of disease results from the unfortunate conjuncture of a combination of factors (these might include for example, genetic predisposition, diet, environmental pollutant, occupational exposure, medical intervention, viral infection, lifestyle habits, etc.) which combine over a lifetime to initiate and promote development of the disease. In this sense, each of the factors that are part of the combination for that person was a necessary contributor to the disease process, although it was not sufficient on its own to provoke the disease. Despite the fact that none of the factors were sufficient to produce the disease on their own, each of the contributory factors may be considered to be a cause of the disease. The disease would not have arisen if any of the contributory factors had been absent. This is one meaning of the multifactorial etiology of disease.

The second meaning is that the combination of factors that induce cancer in one person may not be the same as the combination that induces cancer in another person. Indeed, at the population level, there may be many combinations of causal factors for the same disease. Some factors may be common to different combinations. For example, it may be that in one case of lung cancer, the combination of factors included genetics, exposure to air pollution, exposure to radon in the home, and smoking; while in another person, the

combination of factors included genetics, insufficient dietary consumption of anti-oxidants like carotene, exposure to asbestos, and smoking.

Some characteristics of carcinogens and epidemiologic research on cancer: The following characteristics of most known carcinogens provide a framework for some of the thinking behind the design and interpretation of epidemiologic studies of cancer.

- There is typically a long induction period between exposure to a carcinogen and appearance of the disease. Thus, if a study has not allowed for a sufficient passage of time between the exposure and the disease, the result may report that there is no risk, where in fact there is a risk, but insufficient time has elapsed to make the risk visible.
- There is variability in the carcinogenic potency of different carcinogenic agents; some induce much greater relative risks than others.
- For any given carcinogen, the degree of risk due to exposure generally increases as the exposure level increases, but the shape of the dose-response curve may differ from one carcinogen to another.
- Most known human carcinogens were first discovered as such either by means of astute observation of a clinician noticing a cluster of cases among people who shared a common characteristic (such as working in a particular workplace) or by means of epidemiological research. In most cases, there was no known mechanism to explain the association at the time. Where the mechanisms have been elucidated, they were usually discovered subsequent to the epidemiologic demonstration of a causal relationship. (Siemiatycki 2014)

4.2 *Bradford Hill “guidelines”*

Because of the complexities of epidemiologic research, there has been some concern with how epidemiologic evidence should be used to draw causal inferences. Various authors have written about the types of information that might be considered in assessing whether a body of evidence demonstrates a causal relationship. A set of guidelines, developed in the context of the Surgeon-General’s Report on Smoking and Health (1964) and authored by

Bradford Hill in 1965, has achieved a wide consensus in the epidemiologic community as a pedagogical guide. Hill himself referred to these guidelines as “aspects” or “features” or “characteristics” of an association, and warned against treating them as “hard-and-fast rules of evidence that must be obeyed”. (Hill, 1965) He deliberately avoided referring to them as “criteria.”

Since Hill wrote those thoughts at the beginning of the era of modern epidemiology, without the benefit of decades of practical experience in the way those thoughts were taken up, and how they applied to issues other than smoking and cancer, it is understandable that the practice of evaluation of causality has evolved. A first observation, often overlooked, is that Hill took as a starting point for his writings that chance had been considered as an explanation for the smoking-cancer association and determined to be unlikely. In the historic context of 1964-1965 and the debates around smoking and cancer, this was a reasonable assumption to make, but for any other putative associations, this must be considered. Over the years, respected authors have paraphrased and updated these aspects in various ways, and this will undoubtedly continue. For instance, leading textbooks of epidemiology as well as the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) all have different formulations of Hill’s guidelines.

In the light of 50 years of practical experience after these guidelines were written, and based on my practical experience of evaluating causality in many forums and on many topics, I would paraphrase (and modernize) Hill’s guidelines as follows:

Strength of the association: This can be measured by different parameters, but for cancer studies it is usually measured by the magnitude of the relative risk or odds ratio.

Statistical significance of the association: While this guideline was not explicitly listed by Hill, it is nonetheless in practice an implicit and distinct consideration in assessing causality. If the estimated RR is quite high, indicating a strong association, but is based on a very small study with low precision, this might be solely due to statistical variability. (For instance, when we flip a balanced coin 10 times, we do not always end up with 5 heads and 5 tails. Sometimes, by chance, we may end up with 6 heads and 4 tails. Does this prove that the coin was not balanced?) Evaluating the role of statistical chance as a possible

explanation of the observed association is important. As explained above, the absence of statistical significance is not strong evidence of an absence of a real relationship.

Dose-response relation: If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. There are some counter-examples however where the effect is only observed after a threshold of exposure has been crossed. There are various ways to assess whether there is a dose-response relation. Hill pointed out that the main challenge is to establish reliable and measurable quantification of exposure. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency).

Absence of bias: There are many forms of bias that can infiltrate an epidemiologic study. It enhances the likelihood of a true causal association if we can confidently exclude all the plausible sources of bias explanations for the observed findings. This guideline can also be considered as a component of a guideline to consider other possible explanations for the association.

Temporality: It is clear that the exposure should precede the outcome (i.e. the disease). To ascertain whether the cancer was a result of the exposure or the exposure occurred after the cancer onset seems like a simple thing, but sometimes it can be difficult to ascertain with certainty.

Cessation of exposure: It would add to the credibility of the association if it had been demonstrated that subjects who cease exposure to the agent experience reduced risks of disease compared with those who continue to be exposed. In practice this is an extremely difficult characteristic to demonstrate, partly because of the difficulty or even ethical impossibility of changing people's habits for scientific experimentation purposes. But occasionally there may be a "natural experiment" wherein large numbers of people cease their exposure and the effects can subsequently be measured in an epidemiologic fashion.

Specificity of the association: It was believed that individual risk factors have specific pathological effects, and Hill posited that if we observe that a given agent is associated with

many different pathologies, it increases the likelihood that these are somehow spurious observations, resting on some type of bias in the studies of that agent. In reality, this Hill characteristic has fallen out of usage in the intervening years with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

Consistency of findings between studies (or replication of findings): Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship.

Coherence with other types of evidence: In the case of tobacco and cancer, it was seen that the historic trend in lung cancer mortality rates in the US and UK followed quite closely the national trends in consumption of tobacco, with a 20 year lag. This was interpreted by Hill as corroboration of the results observed in case-control and cohort studies. Epidemiologic evidence of coherence could conceivably take many forms, and the opportunity to assess coherence is something that is specific to the factor under investigation. Assessment of coherence with historic mortality trends would only be possible in the case of a factor whose exposure in the population changed quite dramatically over time in a way that can be documented, and for which the attributable fraction of the disease due to that factor is very high. This was the “perfect storm” of circumstances that allowed for an assessment of the tobacco-lung cancer association by means of time trend correlations.

Analogy: Hill reasoned that if a factor is somehow similar to another factor that has already been shown to be a risk factor for the disease, then it increases the plausibility of a similar impact due to that putative factor. This is such a vague guideline, with no clear implementation suggestions, that it is not often referred to and rarely implemented.

Biologic plausibility: This guideline can encompass many dimensions of information, including physiology (can the agent or its metabolites reach the organ?), animal carcinogenesis (does the agent produce tumours in experimental animals?), cell studies that reveal mechanistic data, and other biologic information on the toxicology of the agent.

Implementing Hill's guidelines: As Hill himself insisted, sophisticated users of these guidelines do not use them as a formal checklist. He summarized his views as follows:

« What I do not believe ... is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? »

The authors of the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) clearly stated that Hill's guidelines are not formal criteria, but rather are more in the nature of a memory aid to help us review the evidence about any given causal association. They stated it this way: "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines."

I have served on many panels to review evidence of causality on one topic or another, including on several IARC Monograph panels that reviewed evidence of carcinogenicity. The IARC process, like the others I have participated in, does not use the Hill guidelines in any rigid formal way. The ideas embodied in Hill's guidelines permeate our thinking about how to evaluate causality, but the operationalization of these guidelines is specific to the problem and to the expert making these determinations. Thus any suggestion that Hill's "aspects" or "features" or "characteristics" of an association should be used as a formal checklist of criteria is simplistic and wrong. To do so would contradict the opinions of experienced epidemiologists, the Manual on Scientific Evidence, and Bradford Hill himself.

In this section, I have laid out and explained the Bradford Hill guidelines in a generic way. Below, in section 8, I will consider how these apply in the context of the talcum powder – ovarian cancer issue.

5. Epidemiologic evidence regarding talc and ovarian cancer

Following some reports in the early 1980's that raised questions about a possible link between use of cosmetic talc powder by women and the risk of ovarian cancer, there were several epidemiologic studies on the topic. By the early 2000's the issue was garnering some attention in the scientific community. The International Agency for Research on Cancer, the premier agency for evaluation of carcinogens, decided to conduct a review of the issue in 2006. Following that review, there have been further studies conducted on the topic.

In the context of a legal action, my mandate is to review all relevant scientific evidence available to date, in order to provide the court with my opinion regarding the link between talc powder exposure and ovarian cancer. The methodology I employed is the same one I have used in my career as an internationally recognized researcher.

5.1 IARC review and evaluation of talcum powder products

As mentioned above in Section 2, the International Agency for Research on Cancer (IARC) is the premier institution in the world for cancer epidemiology and for environment and cancer research. One of its mandates is the evaluation of the carcinogenicity of different agents with which humans come into contact, and this mandate is carried out by the Monograph Programme of IARC. This is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens.

In February 2006, there was such an IARC Monograph meeting to evaluate some agents, including talc. The IARC Working Group comprised 16 highly respected and recognized scientists from around the world; I was asked to Chair the Working Group. We reviewed all

the evidence that was available up to that point in time. This certainly included epidemiologic evidence, but it also included evidence from experimental toxicology, physiology, molecular biology and other domains. The IARC Monograph programme has a formal system for classifying agents. The Working Group must classify an agent into one of the following categories:

- 1 Carcinogen
- 2A Probable carcinogen
- 2B Possible carcinogen
- 3 Not classifiable
- 4 Not carcinogen

After reviewing the evidence, the panel concluded that talc was a “possible carcinogen”, based primarily on evidence regarding the association between dusting powders and ovarian cancer. Here is the definition of this category from the IARC Monograph:

“Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals.”

This 2B categorization was based on the panel’s decision that there was “limited evidence of carcinogenicity in humans”, which is in turn defined by IARC as follows:

“Limited evidence of carcinogenicity in humans: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.”

Subsequent to the completion of the IARC Monograph on talc, a subgroup of the epidemiologists who were on the IARC Working Group, including myself, reviewed the evidence again, but with a view to producing a meta-analysis of the results from the most informative studies conducted to that time. This resulted in the paper by Langseth et al. (2008). This paper was not an IARC publication.

5.2 Information consulted for the present review

In preparation for formulating my current opinions on this topic I assessed, researched, reviewed and consulted a large number of documents, including, but not limited to: all original epidemiological studies published on this topic, all meta-analyses and opinion pieces, experimental toxicology, molecular biology, mechanistic studies, and the IARC Monograph on talc which reviewed all informative studies that had been published before 2006. I was given access to and also reviewed the various expert reports and depositions that have been submitted in various talc cases, either on behalf of the Plaintiff or Defendant, and various internal company documents obtained in discovery.

I systematically reviewed the lists of references of all relevant studies referenced in the IARC report as well as in various meta-analyses and in all recent articles on the topic to identify yet more relevant publications on talc and cancer.

Because some studies have been published in multiple papers and because some papers have included reports on multiple studies, there is not a one-to-one relationship between studies and published papers.

Additionally, I considered evidence regarding the toxicology of talc by reviewing the toxicology evaluation conducted by the IARC Working Group, the summary of talc's putative toxicology referenced in various scientific publications, and the expert reports of various scientific/medical experts in this case.

The central focus of my review is on the epidemiologic evidence.

A complete listing of the documents I consulted, as well as references cited explicitly in this report, is provided in the Bibliography. The Bibliography is in two Parts; Part A comprises all the publications and reports that can be found in publicly available scientific literature. Part B comprises company documents or documents from reports or testimonies of experts.

5.3 My methodology for this review

Table 1 lists the steps I undertook to accomplish my mandate.

5.3.1 Selecting studies for review

To aid in the present assessment of whether or not there is a causal relationship between talcum powder exposure and ovarian cancer, I carried out an up-to-date review of the scientific literature, primarily the epidemiologic literature, concerning the association between use of talc powder and risk of ovarian cancer. This involved meta-analyses to estimate the effect of having ever used perineal powdering, and an assessment of evidence regarding dose-response.

The first task was to find the relevant publications and to set out the distinct pieces of epidemiologic evidence, namely the results of different studies. Based on a number of reviews on the topic of talc and ovarian cancer, including the IARC report, I systematically went through the reference lists to identify all publications that seemed to contain results on the topic. I further conducted a Pubmed search and this did not produce any new informative publications that had not already been identified. In preparation of the meta-analysis, I eliminated from consideration papers that were outside the bounds of what a meta-analysis should contain (i.e. eliminate review articles, commentaries, meta-analyses, and articles that do not really pertain to the issue of perineal talc and ovarian cancer). From the 40 publications that remained, namely those that contained original results on the association between powdering and ovarian cancer, I extracted all results showing RRs between talc powdering and ovarian cancer, and I had these results put into a Filemaker database. This was a value-free exercise. I made no judgement at that stage about relevance or quality of the study or the published results. It was only an attempt to lay out in one “place” the whole of the evidence and to prepare for subsequent analyses. There were over 730 results in this database. On average each publication contained about 18 different RR results of various aspects of talc powder exposure and various types of ovarian cancer. Some contained fewer and some contained many more. (For instance, one study publication contained 180 results, with varying types of ovarian cancer and varying definitions of exposure to powdering.)

In deciding which results to include in a meta-analysis I had to respect the following principles:

- The results have to pertain to the issue of risk of ovarian cancer in relation to use of talc-based powders.
- Where there are sufficient numbers of results to support meta-analyses, there can be meta-analyses for different types of ovarian cancer, and for different routes of exposure to talc-powders.
- In each meta-analysis, each study should only provide one result, so as to avoid double-counting evidence.
- The decision about inclusion of a study should in no way be influenced by whether or not a particular study demonstrated high risks or low risks.

While these seem like simple principles to respect, there were complicating features of the scientific literature:

- Some studies were reported in multiple publications, sometimes the same study subjects were analysed and reported in different ways and sometimes different subsets of the study population were included in different publications. Sometimes the authors fail to clearly enunciate how the data used in one of their papers overlaps with data used in another of their papers from the same study.
- Different studies used different questions about powder use in their questionnaires, and sometimes the same study reported results by different ways of asking about or defining exposure.
- A given study may have presented one result or many results, each addressing a different definition of the talc exposure variable and different way of grouping the ovarian cancer cases.
- Different studies dealt differently with the histologic sub-types of ovarian cancer, sometimes grouping them all, or sometimes separating them, or sometimes reporting both grouped and separate results for different sub-types.

-
- Different studies used different metrics for analysing powder exposure and estimating its corresponding RR.
 - Different studies dealt differently with the challenge of adjusting powder-related risks for possible confounding by other factors.

Decisions had to be made regarding which types of exposure to consider, which types of ovarian cancer to consider, which metrics of exposure to consider and which studies and publications to consider. It is necessary to be rigorous in making such decisions ahead of time, rather than “cherry-picking” results from different studies that appear to support one theory or another.

Appendix Table A1 provides a list of those 40 publicly available publications that have included some original results that might pertain to the association between powdering and ovarian cancer. **Appendix Table A1** shows which publications were included and which papers were excluded from my meta-analyses. For each of the 14 excluded papers, the table also shows the reason. Some papers were excluded because the results did not pertain to ovarian cancer and powdering in the perineal region. Some papers were excluded because the results presented therein were subsumed by a subsequent publication by the same research team or as part of a pooled analysis of multiple studies. Notwithstanding my intention to identify all unique studies and to extract a best “bottom line” result from each study, the nature of the studies and how they were analysed and reported led to many judgement calls. It must be acknowledged that there can be differences of opinion among equally competent and equally well-motivated scientists in how to choose among the different publications and the different results within publications.

Fortuitously, and unbeknownst to me at the time, two other sets of investigators (Berge et al 2018; Penninkilampi et al 2018) carried out separate meta-analyses on this topic at about the same time as I was carrying out mine, and this gives an opportunity to do some cross-comparison of different reviews and meta-analyses. I will comment on these after presenting the results of my meta-analyses.

5.3.2 What were women exposed to in body powders?

Talc has been the main ingredient of body powders used by women over the past century. “Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibers ... Talc may also form as true mineral fibers that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a ‘habit’. Asbestiform talc fibers are very long and thin.”(IARC 2010) The structure of platy talc is characterized by a hexagonal sheet arrangement of silicon-oxygen tetrahedral groups in a common plane which creates a double-sheeted structure. These sheets are easily separated which accounts for the “silky” or “smooth” feel of talcum powder products (IARC, 2010). As a mined mineral, the precise chemical and physical characteristics of talc are in part determined by the particular geological formations from which it is extracted. The local conditions can also produce “impurities” in the extracted talc including asbestos, quartz and various metals. It is claimed that cosmetic talcum powder products normally contain >98% talc (Zazenski *et al.*, 1995) but the purity may have been lower in the past. (IARC 2010) When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained in those products.

Asbestos is a commercial term that comprises six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite. Similarly to talc, these six minerals can occur in a non-asbestiform habit. Some types of asbestos are found in the same geological formations as talc.(IARC 2010)

By the 1970’s it was reported that asbestos fibers were found in commercial talcum powder (Cralley 1968; Rohl 1976), though there was some doubt expressed regarding the quantification of the exposure and the ability to discriminate between asbestiform and non-asbestiform talc. (Krause 1977; IARC 2010) The talc industry was constrained to remove asbestos from talcum powder products. Representatives of the industry have claimed that talcum powders were free of asbestos fibers since the 1980’s (Hopkins 2018; Pier 2018), but this assertion has increasingly come under doubt as number of labs have

reported finding asbestos fibers in talcum powder products. (Blount 1991; Paoletti 1984; Gordon 2014; Longo et al 2017; Longo et al 2018; Blount deposition 2018; Pier deposition 2018) These various studies that have reported finding asbestos in historic talcum powder samples have been challenged by other reports that failed to find meaningful amounts of asbestos in historic talcum powder samples. (CIR 2013; Anderson 2017) These various findings and opinions are somewhat complicated by the fact that both talc and asbestos have varied chemical and physical characteristics and various methods can be used to measure them.

What is clear is that asbestos, and all forms thereof, has been evaluated to be carcinogenic. It has long been recognized that inhalation of asbestos carries with it a risk of lung cancer and of mesothelioma, a cancer of the lining of the lungs, as well as larynx cancer. What has only recently been recognized is that women who are exposed to asbestos experience an excess risk of ovarian cancer. (Straif 2009; IARC 2012) This conclusion was based on five studies; a subsequent meta-analysis reported that the RR of ovarian cancer among asbestos-exposed women was a highly statistically significant 1.77 (1.37-2.28).(Camargo 2011) The route of exposure that generates risk of ovarian cancer among women exposed to asbestos is not clear, but inhalation and migration of asbestos particles to the ovaries has been proposed as a credible biologically plausible mechanism. (Miserocchi 2008)

Among the metals detected in talcum powder products are some which are recognized carcinogens, namely nickel and chromium. It is not known how widespread was the “contamination” of talcum powder products by these metals and how high were the concentrations in the entire commercial production of talcum powder products of the past several decades, and how these exposures measure up to exposures that may cause cancer. However, evidence that asbestos and some other known carcinogens have been detected in some commercial cosmetic talcum powder products and credible mechanisms that such particles can translocate to the ovaries is an important consideration in deriving an opinion on biological plausibility, and I will consider it below in my section on biological plausibility of a causal link between talcum powder products and ovarian cancer.

Alternative formulations of baby powder include cornstarch formulations, which have become available in the past 30 years. It was possible for women to purchase and use cornstarch products or talcum powder products. Most epidemiological studies have not tried to ascertain whether the women in their studies used talc-based or cornstarch-based formulations and many women may have been unaware of the composition of the powders they used at different times. It is impossible to ascertain with certainty from most of the publications whether the reported epidemiologic results pertain to talc-based powders or cornstarch-based powders or both. Those studies that did report results for cornstarch had few women self-reporting use of cornstarch and the risk estimates were rather imprecise and unstable. For those studies that did report separately the findings for talc-based and cornstarch-based formulations, I used the results for talc-based powders. For those that did not make such distinction, I used the results combining all types of powders as reported. If it turns out that there is an increased risk associated with talc but not with cornstarch, the inability to discriminate the two in statistical analyses would have the effect of diluting the estimates of risk due to talc. That is, the RR estimates would be attenuated.

5.3.3 Routes of exposure

Some studies reported results based on particular ways of using the powders, such as on feet or perineal use or use after bathing or use on sanitary napkins or use on diaphragms or use by male partners, and so on. And many studies just reported results for all routes of perineal exposure combined. For my Main analyses, I aimed to use the reported results pertaining to all types of perineal use combined. Where the results were reported for individual routes of exposure rather than all perineal use combined, I identified the one that came closest to powdering in the perineal area from all routes.

The number of studies providing results pertaining to any of those specific routes of exposure was much less than the number providing evidence for all routes combined and insufficient to provide reliable meta-analysis results for route-specific estimates of RR. Among the route-specific reports, the one that had most often reported RR results was exposure from dusting of sanitary napkins. I will conduct a separate meta-analysis regarding the risk of ovarian cancer in relation to use of powder on sanitary napkins.

5.3.4 Questionnaire items on use of talc powders

In the case of exposure to cosmetic talc powder, the most common and realistic way of ascertaining exposure has been to question women. But there are many ways this can be done, and indeed many types of questionnaires have been used. A very simple format that has been used is to ask a question such as “have you ever used powders in your genital area?” But, the validity of the response would be enhanced if the question is framed in a more specific manner, so long as the respondent can be expected to know the answer to the more specific question. One possibility would be: “have you ever used powders that contained talc on your genital area more than once a week for at least 6 months of your life? This would include powdering your genital area directly or powdering your underwear or powdering your diaphragm or powdering your sanitary napkin.” There are scores of ways such questions can be asked, and there has been variability in the methods of questioning among the different studies of powder use and ovarian cancer. In most studies, the questionnaire question about Ever Use was actually about Ever Regular Use, not Ever Occasional Use.

Among women who used powders, there can be an enormous range of usage from a few occasions in a lifetime to profuse daily usage. Among the many dimensions of talcum powder exposure that might influence the risk of cancer are the following: manner in which the talc was applied, age at which exposure began; if it ended, age at which it ended and years since it ended, frequency of use per day, week or per month, multiple applications including to genitals, undergarments, sanitary napkins, etc., and whether and how that varied at different ages. Some studies have used a single simple question, while others have used scores of questions to get at the lifetime history and many facets of powder use.

While I believe there are quality differences between the different studies in the way talc powder data have been collected, I have refrained from imposing my judgement about the quality of the questionnaire data on the selection of studies to include in meta-analyses.

5.3.5 Metrics of exposure

I used the reported results for the binary metric Ever Regular Use vs Never Regular Use, given the limitations of the available data, and using the investigators' decisions about how best to measure this. While this may seem like a simple tactic to implement, some studies were reported in such a way that in fact I had to make "judgement calls" about which of the reported results came closest to the desired metric.

For "dose-response" assessment, I used three pertinent metrics of exposure: duration (years), intensity/frequency (uses per day, week or per month), and cumulative number of applications, measured sometimes in absolute numbers or sometimes in quantiles. Of the three, the most meaningful is the cumulative number of applications.

6. My meta-analyses regarding talcum powder products and ovarian cancer: data included and results

6.1 Features of the studies

Following the exclusions indicated in Appendix Table A1, **Appendix Table A2** shows the studies that ended up being included in one or more of my meta-analyses, and brief descriptions of administrative and contextual features of each study. **Appendix Table A3** shows, for the same studies, some information about the talcum powder exposure variable and the covariates used by the authors in their control for confounding.

Appendix Table A2 shows that most studies were conducted in the USA. All but three were case-control studies and of the case-control studies, all but four used some type of population control series. Most studies had fieldwork data collection in the 1970's and 1980's; only a few studies started data collection after 2000. Table 3 shows for each study what exposure variable I was able to use to approach the notion of Ever exposed regularly to talc powder in the perineal region. Different studies had different questions in the questionnaire and different studies reported different variables. The questionnaires usually elicited lifetime use that was more than very sporadic, with terms like "regular" use. Only the Gonzalez 2016 study failed to ask about lifetime exposure before the interview; they asked about usage only in the preceding 12 months. The Gates 2010 study

asked about use of talc up to 1982 but not afterwards. Some studies asked separately about different routes of exposure and then rolled them together in statistical analyses, while some rolled all routes of exposure together in their questioning. The term that I show in Appendix Table A3 is the term that the authors reported in their publication of results; it is sometimes rather cryptic. Appendix Table A3 also shows which variables that the authors reported having used as adjustment variables. Sometimes these are variables that were explicitly included in final statistical models, and sometimes these were dealt with in a more indirect way such as a staged analysis in which a screening is conducted using a change-in-estimate procedure.

All meta-analyses were conducted using the well-known package Comprehensive Meta-Analysis Version 3. (Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013; <https://www.meta-analysis.com/index.php?cart=BFZW2135997>)

6.2 Association between binary variable talc powdering and all types of ovarian cancer combined – data and results

6.2.1 Individual studies and results on binary exposure variable

Table 2 shows RR results, as well as the corresponding 95% confidence intervals, for each informative study included in the Main meta-analysis or in any sensitivity analyses. (I will explain this distinction below.) As I explained in Section 4.1, the single number which reflects quite well the statistical strength of a study, be it case-control or cohort, is the number of exposed cases, and I have included this parameter in Table 2. Table 2 shows the RR reported in each study by Ever (regular) use of powder in the perineal region (all routes of perineal exposure including direct powdering on genital area, on sanitary napkins, on underwear and on diaphragms). The table shows results for all types of ovarian cancer combined.

Before conducting any meta-analyses, we can peruse the results in Table 2 to observe certain patterns.

Of the 33 RR results shown in Table 2, two are below 1.0, one equals 1.0, and 30 are greater than 1.0. On the null hypothesis that there is no true association between powdering with

talc and ovarian cancer, we would expect as many of the RR estimates to be above 1.0 as to be below 1.0. The observed distribution (2 below and 30 above) is clearly and strongly in defiance of the null hypothesis. Further if we rank the RR estimates from lowest to highest, the median value, the one in the middle, would be 1.34.

This informal analysis does not take into account that the 33 estimates in Table 2 are not strictly independent of each other. There are various ways to carve out independent sets of results from this list of results in Table 2, and the meta-analyses will be designed to do that. But no matter how the studies are configured, it will be found that one or two of the RR estimates are below 1.0 and somewhere between 20 and 26 are above 1.0. Such an imbalance cannot be due to chance.

6.2.2 Strategy for Main analysis and sensitivity analyses

An investigator typically has in mind a strategy for analysing and presenting the results. There may be some judgement or assumptions involved in deciding on the strategy. The investigator may wish to see how the results would be affected if other judgements or assumptions were made. In other words, how robust are the results to alternative judgements and assumptions. Such alternative analyses are referred to as *sensitivity analyses*.

There were several dilemmas in selection of studies and results to include in the meta-analysis. I made decisions in each case that I believe provides the best basis for a meta-analysis. But in deference to other possible decisions that might have been made, I conducted some sensitivity analyses as well. I list what the dilemmas were and which options were selected for Main analyses and for sensitivity analyses.

a. Terry 2013 and Wu 2015. The Terry 2013 paper brought together data from 8 different research teams. Some of those teams had previously published their results on talc and ovarian cancer and some had not. Normally, a pooled analysis would take precedence over the individual component studies. In this case, however, there were complicating factors. The Los Angeles component study of Terry 2013 (Wu, Pike and colleagues) was conducted in stages and the Terry 2013 pooled analysis only had access to the early stage. Subsequently, Wu and colleagues carried on with their data collection, and published a

more complete set of results from their study in Wu 2015. The Terry 2013 paper contained 208 exposed cases from the Los Angeles study, whereas the Wu 2015 paper contained 701 exposed cases. In the entire Terry 2013 paper there were 2600 exposed cases. Ideally, we would wish to exclude from the 2600 exposed cases in the Terry 2013 paper, the 208 exposed cases that came from the early Los Angeles data. But that information was not available. Thus there is an 8% overlap between the exposed cases in the Terry 2013 paper and those in the Wu 2015 paper.

I adopted the following strategy. For the Main analysis, I included both Terry 2013 and Wu 2015. The 8% overlap of exposed cases is unfortunate but I believe its impact would be trivial, and in any case we will have some empirical evidence of its impact from a sensitivity analysis.

I conducted sensitivity analyses using a different strategy. The Terry 2013 paper contained a table in which the individual results of the 8 component studies were reported. I used the results as reported there for 6 of the 8 component studies, for which the Terry paper contained the latest results. For the Los Angeles study I used the result reported in Wu 2015 which was much more complete than the L.A. study result in Terry 2013. The eighth study was the study of Cramer that was one of the components of Terry 2013 but that was also reported subsequently in Cramer 2016. It is not clear whether the Cramer 2016 paper contains more up to date data than the corresponding component in Terry 2013, but it possibly does.

To summarize, the Main analysis contained pooled result from Terry 2013 and the result from Wu 2015. There were sensitivity analyses that dropped the pooled result from Terry 2013, but included the (apparent) latest published result for each of the 8 components.

b. Nurses Health Study. This cohort study was initiated in 1976 and was not a study of talcum powder products and ovarian cancer. The study involved a wide-ranging annual questionnaire which inquired about many health related issues. In 1982 there was a very succinct question about use of body powders. The cohort has been followed-up to ascertain the occurrence of cancers (or other diseases). There was a publication that contained results on talc and ovarian cancer from this study in 2000 (Gertig 2000); later, after more

years of follow-up there were two further papers presenting results on talc and ovarian cancer (Gates 2008 and Gates 2010). Clearly the Gertig result did not belong in my meta-analysis, since it was subsumed by subsequent analyses, but the choice between the Gates 2008 and Gates 2010 was not so obvious. Gates 2008 was based on a nested analysis of a subset of the cohort that probably entailed better control for confounding. Gates 2010 was based on the entire cohort and thus on a much larger sample size. The two RR estimates from the Gates papers are quite different from one another (RR=1.24 in Gates 2008 and RR=1.06 in Gates 2010). It is not clear whether the difference in results is due to the different design and analytic procedures used in the two papers. The authors did not comment on the inconsistent results.

My Main analysis included Gates 2010 but not Gates 2008. Some sensitivity analyses contained Gates 2008, but not Gates 2010.

It should be noted that whereas I did not use the Gertig paper results in the meta-analysis of Ever / Never Use of talcum powder products, I did use some dose-response results from Gertig because subsequent publications from the Nurses' Health Study did not present such results.

c. Schildkraut (2016). This was a case-control study of ovarian cancer among African American women. The fieldwork and interviewing was carried out from 2010 to 2015. The authors speculated that publicity surrounding two class action lawsuits on talc and ovarian cancer in 2014 may have subsequently induced bias in the validity of reporting of talc exposure. Consequently, in their analysis and report, they presented two sets of results, one for all women in the study, and another for those interviewed before 2014. It is impossible for me to evaluate the validity of the speculation, as it was for the authors. Consequently I will use the results from the entire sample and those from the pre-2014 sample. I refer to the entire Schildkraut study result as Schildkraut A and the pre-publicity result as Schildkraut B.

The Main analysis contained Schildkraut A. Some sensitivity analyses contained Schildkraut B.

d. Shushan (1996). This ovarian cancer case-control study, conducted in Israel, reported results on talc and ovarian cancer, but the report was quite cryptic regarding the data collection and the talc exposure variable.

The Main analysis excluded Shushan 1996. Some sensitivity analyses included Shushan 1996.

6.2.3 Results of meta-analyses on binary exposure variable for all ovarian cancers

Figure 1 shows the printout from the Comprehensive Meta-analysis (CMA) package for the Main meta-analysis for the association between ever regular use of talc powder in the genital area and all types of ovarian cancer combined. 21 RR results were used in the Main meta-analysis, but the Terry 2013 study represents 8 different study teams and 10 distinct studies. In the forest plot, I have ordered the studies in increasing magnitude of the RR estimate. It can be seen that only one study produced an RR estimate to the left of the null value of 1.0, while 19 studies produced an RR estimate to the right of the null value of 1.0.

The meta-estimate of RR is 1.28 with a 95% confidence limit from 1.19 to 1.38. The p-value is too small to register in 2 digits. This is a very highly statistically significant result. The probability of this result being attributable to chance is vanishingly small.

The 21 RR estimates in this Main meta-analysis had a fairly low p-value for heterogeneity, 0.07, but it was not statistically significant. This means that there was considerable variation in RR results across the studies, but this might have been due to chance. That there is significant variation in RR estimates is not surprising. The different studies were conducted among different populations, using different methodologies. It would be surprising if there was no variation. It is nevertheless true that in the current state of knowledge the best estimate of RR is the meta-estimate of 1.28.

Table 3 shows the results of the Main meta-analysis again and contrasts it with the results of seven sensitivity analyses that embody alternative plausible strategies for selecting studies and selecting results within studies. These alternative strategies had almost no effect. The meta-estimates of RR varied in a narrow range from 1.26 to 1.30. Even the lowest of these would lead to the conclusion that there is a highly significant association.

It can be affirmed, quite confidently, that the apparent overall elevated risk for women who had ever used such powders is not an artefact of chance variation. This conclusion is not new. It has been stated by the authors of previous meta-analyses. However, I believe this conclusion is based on the most current and reliable data now available.

From a statistical point of view, each of the studies listed in Table 2, except for one or two outliers, shows a 95% confidence interval that overlaps substantially with the confidence interval of the meta-RR estimate (1.19 – 1.38). Further, the majority of the study-specific confidence intervals (including 2 of the 3 cohort studies) include the overall meta RR of 1.28. This shows that there are few if any studies that are not compatible with the overall RR estimate.

6.2.4 Other contemporaneous meta-analyses on binary exposure variable for all ovarian cancers

I started to conduct my meta-analyses in 2015 and revised it in 2018. Towards the end of my analyses, I discovered that two other teams of researchers were carrying out meta-analyses on the same topic at almost the same time. The simultaneous and independent conduct of these three meta-analyses provides a unique opportunity to cross-validate the methodologies and results. (I knew nothing about the two others and I assume they did not know either about mine or the other meta-analysis.) It is sometimes portrayed that meta-analysis is a fairly automated procedure which should produce identical results irrespective of who carries it out. This is far from true.

Even before the statistical part of the meta-analysis is conducted, the author of a meta-analysis has to assemble all of the relevant data. That usually consists of two steps: identifying all informative studies on the topic and identifying the relevant result from each study to include in the meta-analysis. There are many ways to do these steps, and it is not surprising that different, equally competent, investigators may make different decisions about how to identify the studies and how to identify the most relevant results. This is particularly true in the area of observational epidemiology research, as opposed to clinical trials research. Research designs and methods of conduct and reporting are much more standardized in clinical trials research than they are in observational epidemiology. In the

area of research on talc and ovarian cancer (which is observational) there are many opportunities for judgement of the author of the meta-analysis to come into play, and in section 5.3.1 I have listed some of the decisions that I made, in the way I managed the selection of studies.

The two other meta-analyses were conducted by Berge et al (2018) and by Penninkilampi et al (2018). They conducted rather different search procedures than I did. Since I had already participated in the IARC review and the Langseth 2008 paper, I already had a head start on collecting the relevant scientific literature. **Appendix B** shows a 3-way comparison of the studies that were included in the meta-analyses by the three authors, and the data from each study that were judged to be most relevant by each author.

As a generalization, it can be seen that the three synchronous meta-analyses identified more or less the same studies and that in general they extracted the same result from each study; but this was not always the case. For my own meta-analysis, I was comforted to note that there was no study that was identified by one of the other meta-analyses that I had missed in my search of the literature (Appendix Table A1).

One of the main points of discordance in procedure was how the three analyses dealt with the Terry 2013 study. Namely, in my Main analysis I used the result of the pooled Ever/Never RR that was quoted by the Terry study, and dropped from consideration the various component studies of the Terry analysis. By contrast, the two others (Berge and Penninkilampi) adopted the strategy of using the results of the individual component studies rather than the overall pooled result. Berge 2018 used the results of the individual component studies as reported by Terry 2013, for most component studies, but for two component studies they used results that were reported in publications that gave results with additional cases. Penninkilampi 2018 also used individual component study results rather than the Terry 2013 pooled result. There are trade-offs between these different approaches. I prefer to use the Terry 2013 pooled result for two reasons. First, a pooled analysis with a standard set of covariates and a standard statistical model is considered superior to a meta-analysis of the components study results. Second, each publication tends to show a variety of results, and the author of the meta-analysis has to choose a

“best” one to represent the “bottom line” from each study. In the Terry pooled analysis, it was the investigators of the original studies, who were also co-authors of the pooled analysis, who chose which would be the “best” result to represent the study, and this in my opinion is more reliable than outside authors making that decision.

Table 4 shows the meta-RR results from each of the three meta-analyses. Notwithstanding the differences in choices and strategies of the three meta-analyses, the meta-RR results are quite similar, ranging from 1.22 (1.13 – 1.30) in the Berge analysis, to 1.28 (1.19 – 1.38) in my analysis, to 1.31 (1.24-1.39) in the Penninkilampi analysis. These three sets of results are really quite close to each other.

The methodology I used is sound and reliable and consistent with the high standards of my discipline. The strategy and decisions I made in relation to the studies selected and the data abstracted from each informative study is consistent with that methodology I use in my professional practice, and that has earned me recognitions and honors throughout the world.

The results shown in Table 4, are in the same “ballpark” as the meta-analysis previously conducted by Langseth 2008 and they are based on a larger pool of accumulated publications. This indicates that recent evidence is consistent with older evidence and reinforces the consistency of the evidence.

6.2.5 Meta-analysis on powdering of sanitary napkins

Tables 2-4 pertain to RRs for the combination of all routes of exposure to the perineum, including direct dusting and dusting on sanitary napkins, diaphragms, underwear, and condoms. When such an exposure variable was not provided in the paper, I used the one that came closest, with priority to dusting on the body directly. Most studies did not report RR results for every route of exposure separately. For the studies that did so, the numbers exposed were much lower than for all routes combined and there was limited statistical power in those analyses. Of the different routes, the dusting on sanitary napkins was generally the most commonly reported route apart from direct dusting. Consequently I assembled the data pertaining to dusting on sanitary napkins and conducted a meta-analysis of those results.

Table 5 shows both the individual studies that had results on sanitary napkin dusting and the meta-analysis result for those studies. The meta-RR was 1.08 (95%CI 0.89 - 1.31), heterogeneity $p=0.09$. Given the overlap between the confidence intervals between this meta-RR estimate for sanitary napkin powdering and the meta-RR for powdering the perineal area via any route (1.28; 95%CI 1.19 - 1.38), it cannot be affirmed that the result for sanitary napkins is statistically significantly lower than the meta-RR results in Table 3 for all routes of exposure; but the tendency is in that direction.

Berge 2018 and Penninkilampi 2018 also meta-analysed the data on use of powder on sanitary napkins. By contrast with my results, Berge 2018 reported an RR of 1.00 (95% CI 0.84-1.16) and Penninkilampi 2018 reported an RR of 1.15 (95% CI 0.94-1.41). Since their publications do not make it clear which studies and which results were used in these analyses, I cannot see easily what explains the discordance among the three meta-analyses for sanitary napkins powdering. In any case, it certainly appears that the RR was lower for application to sanitary napkins than it was for general perineal application. The interpretation of this finding is not self-evident. The different routes of exposure may entail very different frequency of exposure. For instance, whereas use of powders on sanitary napkins might involve exposure on only a few days per month, regular use on the perineal region often involves daily or near daily application. I am unaware of any evidence that would address the question of whether regular use on sanitary napkins leads to greater or lesser delivery of talc particles to the portal to the ovary than does regular powdering on the perineal region.

In any case, irrespective of the evidence regarding sanitary napkin exposure, the results in Tables 2 and 3 clearly show an association between exposure to talc in the perineal region and risk of ovarian cancer.

6.3 Dose-response – cumulative exposure, duration and frequency

An important part of the evaluation of causality is to determine whether the results display any kind of dose-response pattern. Tables 6 to 8 show results for various quantitative metrics of exposure.

Trends by cumulative exposure: **Table 6** shows results from five publications that presented results based on a cumulative amount metric. Four of the studies were based on counts of numbers of powderings, while the Cook 1997 result was based on counts of the number of days on which powdering occurred. As can be seen by perusing the column of numbers of exposed cases, the Terry 2013 results dwarf the others in terms of the statistical information they contain. The Schildkraut study, with about one-tenth as many subjects as the Terry study, nevertheless has as many subjects as the other three studies combined. The relative statistical power of the different studies is also manifested in the width of the confidence intervals.

The evaluation of the statistical significance of a trend is not a methodologically straightforward endeavour. Of particular concern is the question of whether or not the test for trend among subjects in different “dose” categories should include or exclude the unexposed category. My view is that it depends on whether or not the study results for Ever/Never exposure are part of the buffet of results presented by the authors. Namely, if the only result presented is a dose-response analysis, then it is appropriate to include the unexposed category as part of the study results. If the Ever/Never result is presented and then a dose-response analysis is conducted, it is preferable to maintain statistical independence of the two analyses by excluding the baseline unexposed category from the dose-response analyses. I will interpret the data from these studies in light of this interpretation of trend tests.

The three smallest studies in Table 6 show no evidence of a dose-response pattern. However, the estimates are so imprecise, as evidenced by the very wide confidence intervals, that they are virtually uninformative regarding the presence or the absence of dose-response.

When looking at the Terry 2013 results, which assemble data from eight teams and 10 studies, the confidence limits are much tighter and the estimates of RR much more precise. The p-value for trend (excluding the unexposed group) is 0.17. Nevertheless, with a reference value of RR=1.0 among unexposed, and with point estimates of RR in four quartiles of cumulative exposure of 1.14, 1.23, 1.22, and 1.32, these results are certainly

compatible with the presence of an underlying dose-response relationship. Note that the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response. Similarly, the Schildkraut 2016 study results, while based on only two lifetime cumulative “dose” categories with point estimates of 1.16 and 1.67, are also compatible with a dose-response pattern.

Trends by duration of exposure: **Table 7** shows the results of those studies that presented RRs by duration of use. The Terry 2013 pooled analysis did not report results by duration of use; however, some of its constituent studies did so and are included here. The numbers in each of the duration categories in each of these studies is quite small, and consequently the RR estimates are very imprecise, with wide confidence intervals. The categorisation of duration differed quite a bit among the studies and it is not easy to compare results between studies. There is no indication of a dose-response relationship in these results. Though, the wide confidence intervals make it impossible to affirm that there is evidence against dose-response. Further, the largest study showing results by duration of use, Wu 2015, did find a significant increase in risk with increasing duration.

Trends by intensity of exposure: **Table 8** shows results of those studies that reported by intensity (i.e. frequency) of usage. This ignores duration of usage. Like the results in Table 7, the results in individual studies are based on rather small numbers and they entail imprecise estimates of RR. Also like Table 7, the pattern of results is equivocal. There is no clear evidence for or against an underlying dose-response.

The Berge 2018 paper also looked at dose-response. They only looked at trends by duration of usage and frequency of usage, analogous to my Tables 7 and 8. However they actually fitted continuous variable models and found that there were significant trends in risk by duration and by frequency of exposure. They did not examine trends by cumulative exposure, and in particular they did not use the results from the Terry 2013 pooled analysis, which in my view is the most informative evidence available on dose-response.

Penninkilampi 2018 looked at risk according to long duration of usage and found no trend. They also looked at cumulative exposure with total number of applications, and they reported a slightly higher RR for women with greater than 3600 applications (RR=1.42)

compared with women who had fewer than 3600 applications (RR=1.32). I cannot determine from the paper which studies were included in this analysis and in particular whether the pooled Terry 2013 dataset was included. While the Terry 2013 and Penninkilampi 2018 papers both contained some results on dose-response, they are not included in Tables 6-8 because they are not original data collection studies; like mine, their's is a review of other studies which are contained in Tables 6-8. As indicated above, all other things being equal, the best metric of the three quantitative ones is the cumulative exposure metric, and that is the one that happens to provide the most statistically reliable data. Thus, the evidence from Table 6 overrides the weaker evidence from Tables 7 and 8. The evidence from the Terry 2013 paper is the most important piece of evidence we have on dose-response. The evidence from the Terry 2013 paper is compatible with the presence of a dose-response relationship between use of powder and ovarian cancer.

6.4 Subtypes of ovarian cancer - in particular, serous invasive tumors

Most studies that provide results on RR between talc powder and ovarian cancer provide results for all types of ovarian cancer combined. Less than half of the published studies have also provided results of the associations between talc powder exposure and various subtypes of ovarian cancer.

To the extent that talc exposure might have different effects on different subtypes of ovarian cancer, there would be a clear advantage to segregating the evidence by type of ovarian cancer and evaluating the evidence for each subtype. The serous-invasive subgroup comprises over half of all cases, and the rest are split among several other histology-behaviour subgroups (mucinous, endometrioid, clear cell, others, and these can be further subdivided by invasive or borderline). Those latter subgroups entail very small numbers each and barely provide enough data, in most studies, to produce informative risk estimates. In those studies, where results were presented by histologic-behaviour subgroups, it is my judgement that there is no strong consistent pattern indicating that one subtype has higher risk than another. Of course, there is variability in point estimates of RR, but on the one hand the variability in RR estimates between ovarian cancer subtypes within studies is not greater than would be expected from chance variability (mostly, the

confidence limits overlap considerably), and on the other hand, from study to study, it is not always the same subtype that seems to have the highest or lowest relative risks.

In the largest assembly of cases subdivided by histologic subtype, the Terry 2013 pooled analysis, the results by subtype were as follows:

- Serous: n=1197; RR=1.24(1.13-1.35)
- mucinous: n=94; RR=1.06 (0.82-1.36)
- endometrioid: n=304; RR=1.20 (1.03-1.40)
- clear cell: n=187; RR=1.26 (1.04-1.52).

Other than serous invasive tumors, there is no other subtype for which there are sufficient numbers of studies and sufficiently precise estimates of RR in each study to provide reliable estimates of the overall RR. While the results for endometrioid and clear cell tumors show risks that are closely aligned with those for serous tumors, the result for mucinous tumors are so imprecise, because of the very small numbers of such tumors, that the estimated RR of 1.06 is very unreliable.

Consequently, and because there were multiple studies apart from Terry 2013 that presented results for serous tumors, I decided to conduct a meta-analysis for serous/invasive ovarian cancers, but not for other subgroups. The meta-analysis on serous invasive tumors will indirectly inform us also about the relative risks for other types of ovarian cancer. Namely, if the RR for serous invasive tumors is similar to that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) will not be very different from the overall RR. If the RR for serous invasive tumors is much greater than that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) are lower than the overall RR. Similarly, if the RR for serous invasive tumors is much lower than that for all ovarian tumors, it will

imply that the risks for other types (the complement of serous invasive tumors) are higher than that for all ovarian cancer.

Table 9 shows all the studies that reported results concerning the link between talc exposure and serous/invasive tumors. There were 8 informative studies, including Terry 2013, which carried by far the most statistical weight. The meta-RR estimate for serous/invasive tumours was 1.25 (1.1.15- 1.36). This is very similar to meta-RR for all ovarian tumors, albeit based on a smaller number of informative studies. Thus there is no persuasive evidence in these studies, taken as a whole that the effect of talc differs by histologic subtype of epithelial ovarian cancer. That is, with such a tiny difference in RRs between that for all ovarian cancers combined and that for serous invasive ovarian cancers, it can be safely inferred that the RR for other types of ovarian cancer (the complement of serous invasive) would not be far from the overall RR of 1.28.

6.5 Conclusion from meta-analyses and dose-response considerations

My opinion, based on up-to-date data and meta-analyses, is that the RR between ever perineal use of talcum powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). This result is highly statistically significant.

We can rule out random variability as a possible explanation for the apparent excess risks. Further, the examination of results according to the “amount” of exposure, and notably the cumulative exposure variable used by Terry 2013, shows that the higher the exposure, the higher the risk.

Such a pattern of findings can have only two possible explanations: it must be the result of some sort of bias or confounder that operated in multiple studies or it must be the result of a real causal association.

7. Misconceptions and possible biases

In reaching my opinions, I have objectively looked at the data and scientific literature and considered the points of view of others who do not share the conclusions I have reached. There are generally two sources of disagreement: misconceptions of epidemiologic or

statistical concepts which I address below in Section 7.1 and professional judgement of the likelihood of errors and biases in the various epidemiological studies, which I address in Section 7.2.

7.1 Some prominent misconceptions in reviewing the evidence

Table 10 lists some prominent misconceptions, and I will address them here.

Misconception: "Cohort studies are more valid and informative than case-control studies."

As can be seen in Table 2, the case-control studies tended to produce higher RR estimates than the cohort studies. It has sometimes been claimed that cohort studies are more valid than case-control studies. There is no theoretical or practical reason why such a blanket assertion should be universally true. There are many factors that influence the validity of a particular result in a particular study and it cannot be reduced to any simplistic assertion that cohort studies are more valid than case-control studies, or vice versa. In the next section, I will go through a number of potential sources of distortion of results from epidemiologic studies, and I showed that some of them might occur in cohort studies, some in case-control studies, and some in both. Some of these distortions very likely occurred in some or all of these studies that provide data on talc and ovarian cancer. On balance, I believe the results of each of these case-control studies concerning female use of powders and ovarian cancer are credible, and perhaps more so (for reasons given in section 7.2), than the analogous results of each of these cohort studies.

Misconception: "Hospital-based case-control studies are more valid and informative than population-based case-control studies."

In a case-control study, the design objective is to define a study base, or a population base, in which the cases might occur, and to identify representative samples of cases and of controls in that study base. The purpose of a control group is to provide an estimate of the prevalence of exposure to the factor under study in the base population that gave rise to the cases. In many instances, the best source of controls for case-control studies is a population list of some sort. But sometimes using a population list is not feasible or

desirable, and an alternative can be to select controls from among hospital patients with conditions other than ovarian cancer. This was done in some of the ovarian cancer case-control studies.

The most common generalization made by epidemiologists is that population-based case-control studies are more valid than hospital-based case-control studies. In fact, neither this nor the opposite statement that I articulated as a Misconception, is universally correct. Validity of a case-control study depends on the specific design features and circumstances of the study.

It is possible that some types of hospital controls have patterns of usage of powders that are different from those of women in the general population, either because the powders are actually causally associated with the diseases that those women have or because their disease or condition that led them to be hospitalised induces some women to take up the use of such powders. If such a mechanism was present in a hospital-based case-control study, it would likely lead to an artificially attenuated RR, not an artificially inflated RR.

Misconception: "Counting the number of statistically significant results is a valid way of assessing consistency of results among multiple studies."

This misconception betrays a lack of understanding of statistical significance. As can be seen in Table 2, several of the individual studies listed in my meta-analysis did not find a statistically significant increase in RR. This has been cited by some as evidence that there is no real causal link.

In fact, meta-analysis is a method that was developed precisely because counting significant results is an invalid way of synthesising knowledge. Namely, a result from a single study may fail to achieve statistical significance either because there is no risk in that study, or because the statistical power of the study was limited. Meta-analysis was developed in order to combine evidence from multiple studies that may be under-powered on their own, but when combined show an effect that might be statistically significant. The meta-analysis cannot conjure a statistically significant meta-RR if the individual study RRs do not systematically lean in the direction of an excess risk, and they do so in the area of talc and ovarian cancer to a degree that cannot be explained by random fluctuation.

Misconception: "You cannot prove causality with an RR less than 2.0."

There is nothing in epidemiologic theory or practice that justifies such a statement. Indeed, this assertion about an $RR \geq 2.0$ threshold does not exist in epidemiology. There are many well-established causal relations where the RR is less than 2.0. Table 11 lists a number of such examples. In clinical medicine also, it is very common to strive to find therapies that reduce the risk of death from some disease by as little as 10%, and several such discoveries are well documented and have been integrated in medical practice, even though the change in risk is small.

Misconception: "If a product has been used for a long time it must be safe."

It has been argued that since talc powder has been used for many decades by millions of women (and men and children), it has stood the test of time and should be considered safe. This is a specious argument.

Most agents in our environment or in our lifestyle which are now considered dangerous were used for decades or centuries without falling under a cloud of suspicion. These include such factors as cigarette smoking (many cancers and cardiovascular disease), asbestos (lung cancer), sunlight (skin cancer), ingesting very hot liquids (esophageal cancer), and many others.

Misconception: "Government agencies provide the most reliable and authoritative statements regarding the lack of carcinogenicity of talc."

Various national and international agencies have websites which list carcinogens. Examples are: National Cancer Institute (NCI), National Toxicology Program Report on Carcinogens (NTP-RoC), International Agency for Research on Cancer (IARC). It can be argued that these agencies, which undoubtedly have scientific credibility, would not put on their websites information that is out of date or invalid. However, that claim is false.

IARC has a rigorous evaluation process which is considered quite authoritative throughout the world, including in the U.S. But the evaluation is carried out at a certain point in time. The last time talc was evaluated by IARC was in 2006. Based on the evidence available then, the panel rated talc as a "possible" carcinogen. Additional evidence has been accumulated

and come to light since then, but there has not been a new evaluation by IARC. (There are potentially thousands of agents to evaluate, and IARC has resources to only evaluate a few each year. Thus they cannot keep re-evaluating the same ones as soon as new evidence is published.)

NTP-RoC is a congressionally-mandated program whereby the agency is obligated to periodically publish lists of known and suspected carcinogens. Unlike IARC, it appears that the people who make the decisions are internal RoC scientists, rather than external experts, with advice from outside experts. Also unlike IARC, the biennial reports only contain listings of those agents that have been deemed to be definite or likely carcinogens, so there does not seem to be a statutory listing of all agents that have been considered. From the minutes of a meeting of the Board of Scientific Counsellors of NTP held in 2000, it appears that the issue was deferred. I am not aware that the RoC has conducted a subsequent review of talc; although, when renominated in 2004, NTP deferred to IARC.

NCI provides a website for doctors where they indicate for each type of cancer, what are the known risk factors. Based upon my understanding, they do not carry out a rigorous evaluation along the lines of the IARC evaluations or even the NTP evaluations. It is a rather superficial process compared with the IARC process and it depends on the existing knowledge of the committee members which in a short time opines about possible associations between each of the scores of cancer types and scores of potential risk factors. This is not to argue that the members of these committees are less expert than the members of the IARC committees, but the NCI committee members have a short time (apart from their main jobs) to review hundreds of possible factor-cancer associations, whereas the IARC committee members have weeks to review just a few.

Scientists and public health agencies regularly consult the IARC evaluations and those of the NTP. The NCI website for doctors is not considered an up-to-date and cutting edge source of information. This is, of course, no reflection on the gravitas of the NCI as a whole, which has much more invested in its original research mission than in its website for doctors.

There are other organizations which may put some information about causes of cancer on their websites. Importantly, I have not seen any agency or organization, including the FDA, that conducted a rigorous evaluation of the epidemiologic and non-epidemiologic studies like we did at IARC in 2006.

Misconception: "A biological mechanism must be proven before we can establish causality"

There are innumerable examples in medical history of discoveries of risk factors or treatments that did not require knowledge of the mechanisms of pathogenesis in order to determine causality. I have compiled a few such examples from medical history and show them in **Appendix C**.

Very often, the initial suggestion was met with scepticism from the vantage point of biologic plausibility. In fact, very seldom have the essential features of biologic plausibility been worked out by the time the epidemiology has convincingly demonstrated that the association is causal. This can be asserted for the early discoveries such as the cancer causing effects of certain chemicals in dye production facilities, certain metals in various heavy industry facilities, certain emissions of combustion of fossil fuels, ionising radiation, and even cigarette smoking. In most of these examples, it was decades after the epidemiologic evidence became convincing that credible mechanistic theories were proven; though, for some, the biologic mechanisms remain unknown.

Indeed in the guidelines of the IARC Monographs, it is stated that if there is "sufficient" evidence of a risk of cancer from epidemiologic studies, then irrespective of the evidence from animal experimentation and other biologic evidence, the agent in question should be considered a Group 1 carcinogenic agent. My point here is that the demonstration of a proven biologic mechanism is not a prerequisite for demonstrating that an agent is a human carcinogen. Reliable empirical epidemiologic evidence of an association is a sufficient basis for demonstrating causality; the presence of a credible biologic mechanism enhances the degree of proof, though that often lags decades behind the general recognition of causality, as exemplified by the examples in Appendix C.

It is not my opinion that we should ignore or set aside consideration of biologic plausibility. As Hill (1965) indicated in outlining the thought process for establishing causality, biologic plausibility is one of the dimensions to be considered. But, he also cautioned that, “this is a feature I am convinced we cannot demand”. Thus, as I have done in other contexts in regard to other putative carcinogens, I am able to draw causal inferences about talc irrespective of whether a causal mechanism has been proven.

Misconception: “Bradford Hill criteria comprise a checklist of necessary conditions”

As I explained in section 4.2, the “aspects” that Hill listed are not “criteria” and they are not necessary. This point has been made and is widely accepted by epidemiologists. The list of “aspects” in Hill’s original paper have been rephrased and reworked in many textbooks and by most agencies that refer to them. They provide a framework and not a checklist.

7.2 Alternative explanations - Biases and errors

Before inferring that the strong statistical evidence that use of powder in the perineal area by women is associated with ovarian cancer may represent a causal relationship, I considered alternative explanations for these observations. In this section I will consider a number of potential sources of distortion of the risk estimates, under various rubrics. Some of the potential sources of distortion are unique to cohort studies, some are unique to case-control studies, and some can affect both types.

7.2.1 Bias due to non-response or non-participation

This is a potential source of bias in case-control studies.

Among all potential cases and controls who meet the study’s eligibility criteria, some participate and some don’t. The most common reasons for non-participation are: refusal; inability of the researchers to contact the person because they moved or are too sick or died or are otherwise unavailable; if access to the subject is via the treating physician or medical staff, there could be obstacles at that level. If the factor under study, hygiene powder use, is correlated with the likelihood of participation and if the participation rate is low, this could lead to biased estimates of RR. Such bias could artificially inflate or deflate the RR depending on how the various variables are related to each other. If response rates

are low, say below 70%, and differential both by case-control status and by exposed – non-exposed status, this could lead to biased RR estimates. For such a bias to explain the outcomes seen, it would require quite strong associations between likelihood of participation and powder use, and quite strong differences in such associations between cases and controls. In my opinion, it is very unlikely in the context of these studies that response rate differentials would be great enough to induce such large bias.

7.2.2 Recall or reporting bias

This is a potential source of bias in case-control studies.

Because the exposure history is collected retrospectively, it is subject to both non-differential recall errors (see below), and to recall or reporting bias between cases and controls. Cases and controls may have different motivation and proclivities to recall and report use of powders. If it were true that cases had a greater tendency to over-report powdering history or if controls had a greater tendency to under-report powdering, then this would lead to an artefactual exaggeration of the RR.

There are a few possible causes of such differential reporting. First, it might be hypothesized that there is a general tendency for cases in case-control studies to acknowledge behaviours or exposures with much greater frequency than controls just because they are more invested in the research than are controls. They may wrack their brains during the interview to find instances of the queried behaviour or exposure that controls don't pay much attention to during the interview, because the controls just "want to get the interview over with". If this were the case, we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies. But in my experience, this does not occur. (I have conducted many case-control studies, each study eliciting information on many lifestyle factors and exposures. It has not been the case that cases systematically report more exposures than controls.) Furthermore, and more pointedly, if such a phenomenon were operative in these case-control studies of ovarian cancer, we would see elevated RRs when women were questioned about the use of powders on other parts of their bodies than the perineal area. In fact, several studies did ask such questions. In the Terry 2013 analyses, based on very large numbers of women, the

overall RR for ever use of hygiene powder on non-genital areas of the body was 0.98 (0.89-1.07), in stark contrast to the analogous result for genital use of 1.24 (1.16-1.33). In other words, when questioned about powdering in non-genital areas, controls were as likely to say “yes” as cases. Clearly there was no tendency for cases to indiscriminately report exposures more frequently than controls.

A second possible reason for such a situation to arise is if there was widespread knowledge about powdering being under suspicion for ovarian cancer. In such a situation women who have heard about this might internalize the notion that powdering may have caused their cancer, and they might ruminate with such intensity on the notion that they might imagine that they had used powders at some point in the past. But for most of the period of data collection in these studies, there was very little public discussion of a possible linkage between powdering and ovarian cancer and I doubt if more than a handful of the thousands of women interviewed in these studies would have heard of such a hypothesis before being interviewed.

In my opinion recall bias is not likely to have produced the kinds of RRs we see in these studies.

7.2.3 Non-differential (or random) error in recall or reporting of exposure to powders

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

Reporting past history of activities and exposures is always subject to some degree of error; it can result from ambiguity or misunderstanding of the questions, failures of memory, or inattention. And this is certainly true for history of powdering. If such error is non-differential (i.e. equally present for cases and controls in the case-control context) it has an effect on RR estimates that is rather predictable. Namely, as I explained above, it has the effect of artifactually decreasing the RR. The degree of attenuation is roughly proportional to the degree of error or misclassification. If there really is a causal association between powdering and ovarian cancer, then we can be rather certain that the true RR is higher than what we can see in the various studies that have reported RRs.

Furthermore, we might make some reasonable inferences about the impact of reporting error on dose-response trends as well as on the overall RR. It is reasonable to surmise that the amount of reporting error is quite a bit higher for the details of past usage (duration of usage, intensity and frequency of past usage) than it is for the simple fact of usage. That is, there is less error in a woman's report of whether or not she ever used powders on a regular basis than in her report of the details of the usage, even if powdering behaviour may be a relatively stable habit. The consequence of this is that the RR based on ever/never usage (Table 2) is less subject to artefactual attenuation than the RRs based on categorizing the duration or intensity or cumulative amount of usage (Tables 6-8). This is a possible explanation of why there has been a much clearer signal of elevated RR for ever/never usage than there has been for dose-response.

There is likely to be more measurement error of exposure to powders in cohort studies than in case-control studies, for several reasons. First, because the cohort study questionnaires attempted to broach topics that could be relevant to many types of cancer and indeed many diseases, the questions posed in the cohort study questionnaires about talc powder use tended to be much briefer and probably less effective at eliciting valid information than the questionnaires used in case-control studies of ovarian cancer. For instance, the cohort studies did not elicit information on timing or duration of past usage, and one of the cohort studies did not even attempt to elicit information about use of talcum powder products over 12 months before the interview. Second, whereas a case-control design involves a woman looking backwards over her life from the time of incident cancer onset and thereby addressing the entire relevant period of potential exposure, the woman in a cohort study reports on her past usage as of a certain point in her life, but there may be 10-20 years subsequent in which her habits could have changed, and of which the cohort study has no knowledge. The women in the cohort studies were "locked into" their exposure category at baseline of the cohort study. If there were women who in fact started using powders after the baseline, they would be incorrectly labelled as non-users. And, if there were indeed a risk associated with use of talc powders, the risk estimate would be diluted by the incorrect inclusion of users among non-users. Accordingly, the longer such subjects are followed, the more likely such misclassification is to occur.

The age at which information is collected is a relevant consideration. In most case-control studies, the mean age of the study subjects was between 50 and 60. In the NHS cohort study the mean age at baseline questionnaire was around 40 and in the WHI it was over 60. In each study, women were asked about their past history of powder usage. Clearly the WHI women had a further stretch of time to consider than the women of the NHS and even of the case-control studies.

A particular form of measurement error may well have occurred in the Gonzalez 2016 study and produced even more attenuation of RR estimates. Namely, in their brief questionnaire on talc exposure, the question was formulated to ask women about their use of powders in the 12 months preceding the interview. While exposure to talc over the past 12 months may be correlated with exposure over the entire etiologically relevant period, which might go back decades in the life of the woman, the correlation is probably weak, and this is another source of measurement error.

7.2.4 Short follow-up periods for disease ascertainment

This is a potential source of bias that would affect cohort studies.

In a cohort study, if the period of follow-up after baseline is relatively short; and if the latency period between exposure and cancer is long, the excess risk may not be detectable because cases that would occur after long latency have not had time to occur. If this did occur, it would lead to an artificially low RR estimate.

This could have been an issue in the initial publication from the NHS, the Gertig 2000 paper. As of the Gates 2008 and Gates 2010 analyses of the NHS, the follow-up period was probably long enough and this bias should have abated. For the WHI study it was likely an issue in the Houghton 2014 paper, and it would remain so until there is much longer follow-up. It would also be an issue in the Gonzalez 2016 paper from the Sister Study, which had only 6 years of follow-up after exposure was ascertained.

7.2.5 Diagnostic error

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

The diagnosis of cancer is never error-free. And details of histology and staging are even more error-prone. Further, there are trends in diagnostic criteria and methods over time, as well as in the terminology and classifications used. So what we observe in these various studies of ovarian cancer represents imperfect estimates of true biologic/pathologic status. The impact of such “errors” is mainly the same as exposure measurement error, namely it would tend to artificially reduce RR estimates. Since most case-control studies start from hospital-based cancer diagnoses as the point of entry, they usually have reasonably valid diagnostic information.

In general, cohort studies tend to be more vulnerable to this source of error and bias, because disease diagnosis information is often obtained from sub-optimal sources, such as the information provided by the study subject or her family, or information obtained from death certificates. In the three cohort studies included in the meta-analysis, there were high quality verifications of diagnostic information that had been provided by the women or their families. But such verification may not be as reliable as information coming straight from hospital pathology or oncology services. I expect that this was not a major issue here, but to the extent that it did operate, it too would have led to some additional attenuation of RR estimates, as I explained above.

7.2.6 Initiation of powdering as a result of ovarian cancer

This is a potential source of bias that would affect case-control studies.

It has been speculated that women with early symptoms of ovarian cancer might take up the use of powders to help with relief of their symptoms. If so they might report that they used powders before their cancer was diagnosed and this could artificially inflate the RRs. While the women are usually questioned about the period before their cancer was diagnosed, there could be some “telescoping” so that women who start dusting after diagnosis respond in the affirmative to the questionnaire.

In the same vein, it has been speculated that treatment for ovarian cancer might produce side effects that could be relieved by powdering. And again, it might be posited that women ignore the instruction to refer the exposure question to the time before the onset of the cancer.

If the early symptoms of ovarian cancer provoke some women to start dusting the perineum to relieve some of the discomfort, or if the treatment provokes women to start dusting, this would lead to an artefactual excess RR.

I have not found any empirical evidence to support this hypothesis.

In the few datasets I have seen which describe the age distribution of initiation of powdering, there were very few patients who started in the year or two before diagnosis of the cancer. I am inclined to believe that it is virtually a non-issue, and that if it operated at all, it would only have operated on a handful of the thousands of women who were part of the various case-control studies.

7.2.7 Confounding

This is a potential source of bias that would affect both case-control and cohort studies.

If women who use powders are also more likely to be exposed to other risk factors for ovarian cancer, then it might distort the relationship between powdering and OC. The direction and the degree of distortion (bias) that would be induced depends on two components, a) the true association between the confounder and ovarian cancer, and b) the association between the confounder and dusting behaviour. Thus, depending on the direction of these two component associations, the confounding can result in artificially decreased or increased RRs. Typically, the degree of confounding is much lower than the strength of the association between the confounder and ovarian cancer. In order for a confounder to induce an artificial RR of 1.25 for dusting, it would have to have an RR much greater than 1.25 with ovarian cancer and a fairly strong correlation with dusting behaviour. Given that the main studies have controlled for the main risk factors, I consider it unlikely that this operates. Table 1 shows the covariates that were controlled for in each study, and while there is some variability between studies in the list of covariates, the main known potential confounders (age, BMI or weight, parity) have been controlled for in almost all studies. It should be noted that while smoking is a well-established risk factor for many types of cancer, it is not a risk factor for ovarian cancer; thus, there is no need to control for smoking status in studies of ovarian cancer.

A thorough and reliable investigation of potential confounders was conducted by Cramer (2016); in the large database of New England-based studies, they explored the potential confounding effect of a host of personal characteristics including demographic, reproductive, hormonal, comorbidities, activities, and exposures. None of the covariates that they explored had any meaningful confounding effect on the association between talc and ovarian cancer.

7.2.8 Publication bias

This is a potential source of bias that would affect case-control and cohort studies.

This refers to the tendency for some evidence never to “see the light of day”. Namely, when results are “negative” or “null”, it may be that investigators never bother to submit them for publication, or alternatively, that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small. In the talc-ovarian cancer literature this would have been more likely in the pre-2000 era when there was much less scientific interest in the hypothesis linking talc to ovarian cancer. As a sensitivity analysis, I conducted a meta-analysis on the subset of studies in Table 2 that had at least 20 exposed cases. That is, I eliminated the studies from that stratum of the universe of studies that were most susceptible to publication bias. The resulting meta-RR was almost identical to those shown in Table 4. Because this has been a somewhat controversial topic in epidemiologic circles over the past 20 years, I doubt if there were large important studies with null findings on talc-ovarian cancer that went unpublished.

In their meta-analyses, Berge 2018 and Pennikilampi 2018 both showed funnel plots of the results. These are meant to detect so-called publication bias. Both of those analyses concluded that there was no publication bias.

In summary, I consider that the observed association between talc and ovarian cancer is not an artefact due to publication bias.

7.2.9 Summary comments regarding biases and errors

While the results of epidemiologic studies strongly supports the hypothesis of an association between perineal use of powders and risk of ovarian cancer, we must be wary of potential sources of error and bias that can distort an association before concluding that this association is causal. I have therefore gone through the plausible sources and types of error and bias that could potentially explain the positive association seen across the relevant studies to ascertain how likely it is that each such type was actually operative and, if so, what the nature of the impact may have been. These evaluations are based on my professional opinion as an epidemiologist having conducted, reviewed, and evaluated many hundreds if not thousands of epidemiologic studies.

Of the various types of error listed, some could artificially inflate the RR estimates and some could artificially decrease the RR estimates. Some are likely to have occurred and some are unlikely to have occurred. The one that certainly occurred and that has a non-trivial attenuating effect on RRs is random exposure misclassification (section 7.2.3). As explained above, if there is a true association, then the true RR is almost certainly greater than the estimates seen in these studies and in the resulting meta-analyses. Other types of error and bias that are highly likely to have occurred are the two that are specific to cohort studies. Namely, the Nurses' Health Study papers (Gates 2008 and Gates 2010) almost certainly suffered from an attenuated RR estimate because of the compromised reference category of "unexposed" while the Women's Health Initiative paper (Houghton 2014) and the Sister Study paper (Gonzalez 2016) almost certainly suffered from a too short follow-up period (section 7.2.4). In my opinion, the occurrence and the possible impact of other listed types of bias and error are more speculative, and less likely.

Consequently, in my opinion, the observed association between talcum powder products and ovarian cancer is unlikely to be explained by any methodological problems with the studies.

8. Bradford Hill guidelines applied to talc and ovarian cancer

The Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) states: "There is no formula or algorithm that can be used to assess whether a causal inference is

appropriate based on these guidelines.” These guidelines are simply aspects that might be considered in assessing causality. I will give my assessment of how the evidence regarding talcum powder products and ovarian cancer fit into those aspects. I will use the version listed in the Reference Manual on Scientific Evidence. While there is no objective basis or scientific precedent or “scientific jurisprudence” for quantification or weighting of the various “aspects”, to help the reader to understand the relevance that I attached to each “aspect” in my evaluation, I will provide an informal ranking of the importance that I attach to each aspect, in the specific context of the assessment of causality of evidence regarding talcum powder products and ovarian cancer. I will list the aspects in descending order of importance that I attach to them.

My opinions are briefly summarized in **Table 12**.

Highly important aspects in my weighting

There is a set of B-H aspects that are utterly inter-related and cannot be disassociated one from the other. In combination, they represent the most important aspect to consider in evaluation of causality of talcum powder for ovarian cancer. These include strength of association, dose-response, consideration of biases, and consistency of findings.

Strength of the association. This can embody both the magnitude of the RR and its statistical significance. The meta-RR estimate is 1.28. That means that the best estimate from the epidemiologic literature is that women who regularly used talcum powder products in the genital area had 28% higher risk of ovarian cancer than women who did not use such powders. As I illustrate in Table 11 with a few examples, this RR is in line with many well-recognized risk factors for cancer and other diseases. For example, it is well accepted now that people living in an urban neighborhood in which the air is highly polluted with particulate matter have between 5% and 10% excess risk of lung cancer compared with people living in a less polluted urban neighborhood. Also, it is well accepted now that workers exposed to a solvent called trichloroethylene have about a 40% higher risk of kidney cancer compared with workers not exposed to trichloroethylene. Thus, the 28% increase of ovarian cancer for women who used talcum powders is in line with many recognized risk factors. This increased risk as manifested by the meta-RR is highly

statistically significant. (Note that the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts.) Such a high and significant meta-RR could not have occurred by chance. This is a very important factor in how I view the evidence of causality, and it supports causality.

Dose-response relationship. If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency). The most sensitive of these metrics is the cumulative amount. I evaluated the published studies reported on risks according to the different metrics. By far, the most important set of results on dose-response is that from the Terry 2013 pooled analysis of 10 studies using the cumulative exposure metric. And, the next most important from a statistical weight point of view is that from Schildkraut 2016. In both of those studies, there is a clear indication of increasing risk with increasing cumulative exposure. Since the statistical power to detect a trend is less than the power to detect an overall risk, it is not surprising that the p-value for trend does not attain the conventional 0.05 level, but it remains true that these studies support a dose-response. This is an important consideration in my assessment of causality, and the evidence on dose-response that our IARC committee had available in 2006 was much less persuasive than the evidence available now.

Consideration of alternative explanations - absence of bias. There are many potential sources of bias in observational research, including in epidemiology. It is important to consider the presence of bias in each study performed or reviewed in an evaluation of causality. The possibility of bias is so multifaceted that it is impossible to reliably assign an explicit score to the likelihood of bias in a study or in a body of studies. It is also important to understand that identifying a potential source of bias is not tantamount to identifying the presence of bias. In section 7.2, I have reviewed the potential role of several types of biases and errors

that can bedevil such research. I concluded there that none of those factors would cause the apparent associations.

Consistency of findings between studies (or replication of findings). Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship. In my review of the published epidemiological studies and meta-analysis, I am impressed by the consistently elevated risk across studies. Almost all of the 30 or so studies have produced an RR greater than the null (neutral) value of 1.0. If there really were no association between talcum powder use and ovarian cancer, we would expect to see as many RRs lower than 1.0 as higher than 1.0. The pattern we see is like flipping a coin 30 times and getting a heads 28 or 29 times. The individual study RRs are not all necessarily statistically significant, but that is irrelevant because most individual studies did not have sufficient statistical power to detect RR in the range of 1.2-1.4. It is the statistical significance of the meta-RR, representing the combined evidence that has the requisite power, and that excess RR is highly statistically significant. I place great weight upon this evidence of causality and, here, believe it to be amongst the most important findings.

Moderately important aspects in my weighting

Temporal relationship. Exposure should be seen to have preceded disease. It is almost a logical truism. This is the only aspect that Bradford Hill considered to be necessary. In all of the studies I reviewed, the information elicited about talc exposure concerned the time period before cancer onset. Since it is so obviously important, the reader may wonder why I place lesser weight on this aspect. It is simply because the presence of this condition of temporality is so obvious in these studies.

Biological plausibility (coherence with existing knowledge). It is both conventional and natural to consider whether any putative association is biologically plausible. The notion of

biological plausibility is multi-faceted. In the case of talcum powder products and ovarian cancer, it can include such issues as: how such powders have been used, female anatomy and physiology, toxico-kinetics and toxicology of talc, in vitro and in vivo mechanisms of carcinogenesis, and others.

The first thing to note about this aspect that Bradford Hill listed is that it is called “biological plausibility”, not “biological proof”. That is, there was never any implication that a determination of causality should rest on a demonstrated proven biological mechanism. Hill was always reserved about this aspect, stating that it was not an essential prerequisite to establishing causality. As I have mentioned above, it has been common in the history of medicine and epidemiology for the elaboration of a validated biological mechanism to come much later than the discovery and demonstration of a causal association. Appendix C gives a handful of such examples but there are scores more.

Insofar as the issue of talcum powder products and ovarian cancer is concerned, there is evidence to support a few biologically plausible mechanisms. First of all, there are two possible routes that talcum powder products can take to reach the ovaries. There is published evidence that talcum powder products (and its constituents and contaminants) that are applied to the vaginal area can migrate from there to the fallopian tubes and ovaries (Venter 1979; Henderson 1986; Heller 1996) or to pelvic lymph nodes. (Cramer 2007) In addition, as has been hypothesized and partially demonstrated in the discussion of asbestos and ovarian cancer, such particles might reach the ovaries via inhalation and translocation. (Miserocchi 2008; IARC 2012) Once the particles reach the ovaries, carcinogenesis can be triggered by the inflammation engendered by the particles. (Ness 1999; Ness 2000) There is considerable evidence that inflammation is an important mechanism for carcinogenesis (Coussens and Werb 2002; Grivennikov 2010). Alternative plausible mechanisms of carcinogenicity include talc induced oxidative stress (Buz’Zard 2007; Saed 2017; Fletcher 2018), and genotoxicity (Shukla 2009).

The evidence that commercial cosmetic talcum powder products have been shown to contain asbestos, fibrous talc, and heavy metals (Blount 1991; Paoletti 1984; Longo et al 2017, Crowley report 2018) provides a reasonable basis for hypothesizing that these

chemicals may contribute to the carcinogenicity of the talcum powder products. Asbestos is a well-known carcinogen, as are chromium and nickel compounds. It is plausible that any of these, in contact with the ovaries, can be carcinogenic.

The fact that there are credible biologically plausible mechanisms by which talcum powder products can reach the upper genital tract causing an inflammatory response, along with the presence of asbestos fibres and other carcinogens is an important consideration in support of my opinion that the genital use of talcum powder products can cause ovarian cancer.

Aspects of lesser importance in my weighting

Cessation of exposure. It is rare that there is valid evidence available to assess the impact of cessation of exposure in an observational study. In the studies on talcum powder and ovarian cancer, there is no evidence one way or the other concerning the effect of cessation of exposure. This aspect is not applicable and I place almost no weight on it.

Specificity of the association. This aspect is premised on the notion that an agent-disease association is more likely to reflect a causal association if the agent is not also associated with other diseases. In the 1960's, this seemed like a reasonable argument. In light of evidence from the past 60 years, this argument is no longer made and this aspect has fallen out of usage with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

So, I do not place much stock in this aspect. However, if I did, I would have to say that genital exposure to talc is associated with ovarian cancer and no other morbidity, which supports the 'specificity' of the relationship."

Analogy

Hill argued that if the agent is similar to another agent that has been shown to be a cause of the disease, then the agent under investigation is more likely to be a cause. The fact that exposure to asbestos fibers can cause cancers in lung, larynx mesothelial tissue and ovaries (IARC 2012) can indicate that, by analogy, talc, which is similar in some respects, might be

able to induce carcinogenesis. Thus, there is an argument for an analogy between talc and asbestos. While this aspect supports causality in Hill's framework, I consider it much less important an aspect than the ones listed above.

Coherence with other types of knowledge: Coherence with other knowledge can encompass a multitude of possibilities. This aspect is both vague and very open-ended, with no real operational instruction on how to use it. Hill gave an example in his paper, but the example was only applicable to tobacco and lung cancer. This is an aspect that, if it can be demonstrated, can enhance the likelihood of causality, but its absence cannot detract from causality. I don't consider it to have much weight in this context.

9. Contrast with IARC Monograph and other reviews

The 2006 IARC Monograph meeting, which I chaired, found that a causal relationship was "possible" between perineal talc powder exposure and ovarian cancer. I concurred with that evaluation.

It is now my professional opinion, based on the totality of the evidence that, to a reasonable degree of scientific certainty, the causal relationship between perineal talc powder exposure and ovarian cancer is "probable. "

What has changed in the years since the IARC review?

The RR estimates in Table 2 are remarkably consistent in showing a highly statistically significant excess risk. The number of published study results and scientific literature addressing the epidemiology, toxicology, molecular biology, and mechanistic studies has increased since 2006, and the evidence of excess risk has been consistently demonstrated across the past three decades.

The various possible biases that are on the table remain substantially similar to the ones that were considered by the IARC panel. At the time, we were not convinced that the apparent excess risk could be explained by those potential biases or confounding. As stated above, my review of the relevant studies and potential biases has led me to conclude that bias does not explain the consistent increased risks seen across the credible studies.

There is important new information with regard to the issue of dose-response. Contrary to the impression that the IARC panel had of a total absence of dose-response, and even a possible trend in the opposite direction, the results of three recent publications, Terry 2013 and Schildkraut 2016, using cumulative exposure metrics, and Wu 2015 using duration of exposure, all demonstrate a clear compatibility with a dose-response relationship. The recent meta-analysis of Berge 2018 supports the presence of dose-response in both duration and frequency of use. The most convincing of these is the Terry 2013 pooled analysis, which assembled a larger dataset than all other attempts to assess dose-response combined. Clearly, earlier reviews could not have integrated the results from these recent studies.

It is my opinion, based upon the above the data, there is evidence of a dose-response relationship. Penninkilampi 2018 has recently expressed a similar opinion.

10. Conclusion

The totality of evidence demonstrates that perineal or genital use of talcum powder products is associated with ovarian cancer. Based on contemporary data, my estimated RR between ever perineal use of talc powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). The body of epidemiologic evidence is remarkably consistent in demonstrating an excess risk. The evidence summarized in Table 6 is compatible with the presence of a dose-response relationship between cumulative exposure to talcum powder products and ovarian cancer. There are various potential sources of bias in these studies, some of which could have inflated the true RR estimate and some of which would have deflated the true RR estimate. Apart from random measurement error, which is inevitable in such studies and which tends to deflate the RR estimates, there is no certainty that the other potential biases were in fact operative and to what degree. It is my opinion, however, that neither bias nor confounding explains the consistent positive association seen across studies. Additionally, there are biologically plausible mechanisms by which talcum powder products can cause ovarian cancer.

Based on the totality of the evidence, it is my opinion, to a reasonable degree of scientific certainty, that the perineal use of talcum powder products can cause ovarian cancer. Given the seriousness of ovarian cancer and its associated morbidity, this causal risk represents an important public health issue.

11. Tables

Table 1. Steps in my evaluation of general causation between talcum powder product use and ovarian cancer

1. Identify all epidemiology study papers that present results on talc and Ovarian Cancer.
2. Extract all RR results from every paper into a database.
3. Determine which of the papers and results present truly independent relevant results.
4. Extract from each study the RR for Ever/Never use of talc in the genital area in relation to OC risk.
5. Conduct a Meta-analysis.
6. Examine the evidence about a possible dose-response relationship.
7. Consider issues of bias, confounding and other sources of error in the various studies.
8. Consider relevant opinion pieces, review articles, and agency reports.
9. Consider opinions from experts regarding possible biological mechanisms.
10. Consider all relevant aspects of association to infer causation.
11. Write report.

Table 2. Relative risk estimates between ever regular use of talcum powders products¹ in the perineal area and ovarian cancer², from various studies used in the Main Meta-analysis or in one or more of seven sensitivity analyses

Author	Included in Main meta- analysis	Number exposed cases	All tumours		
			RR ³		95% CI ⁴
Booth 1989	☐	141	1.29	0.92	1.80
Chen, 1992	☐	7	3.9	0.91	10.6
Cook 1997	☐	159	1.5	1.1	2.0
Cramer 1982	☐	60	1.55	0.98	2.47
Cramer 2016		642	1.33	1.16	1.52
Gates 2008		57	1.24	0.83	1.83
Gates 2010	☐	231 ⁵	1.06	0.89	1.28
Godard 1998	☐	18	2.49	0.94	6.58
Gonzalez 2016	☐	17	0.73	0.44	1.2
Harlow 1989	☐	49	1.1	0.7	2.1
Harlow 1992	☐	114	1.5	1.0	2.1
Hartge 1983	☐	7	2.5	0.7	10.0

Report on talcum powder use and ovarian cancer

Jack Siemiatycki

Author	Included in Main meta- analysis	Number exposed cases	All tumours	
			RR ³	95% CI ⁴
Houghton 2014	2	181	1.12	0.92 1.36
Mills 2004	2	106	1.37	1.02 1.85
Ness 2000	2	161	1.5	1.1 2.0
Purdie 1995	2	467	1.27	1.04 1.54
Rosenblatt 1992	2	22	1.7	0.7 3.9
Schildkraut 2016 A ⁵	2	248	1.44	1.11 1.86
Schildkraut 2016 B ⁵		128	1.19	0.87 1.63
Shushan 1996		21	1.97	1.06 3.66
Terry 2013	2	2600	1.24	1.15 1.33
Terry-AUS 2013		705	1.13	0.92 1.38
Terry-DOV 2013		272	1.13	0.93 1.36
Terry-HAW 2013		74	0.99	0.70 1.41
Terry-HOP 2013		194	1.34	1.07 1.67
Terry-NCO 2013		195	1.37	1.05 1.80
Terry-NEC 2013		755	1.28	1.12 1.47
Terry-SON 2013		197	1.35	1.03 1.76

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Author	Included in Main meta-analysis	Number exposed cases	All tumours	
			RR ³	95% CI ⁴
Terry-USC 2013		208	1.36	1.06 1.74
Tzonou 1993	☐	6	1.05	0.28 3.98
Whittemore 1988	☐	67	1.36	0.91 2.04
Wong 1999	☐	157	1.0	0.8 1.3
Wu 2015	☐	701	1.46	1.27 1.69

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. In this table we report the result for all types of ovarian cancer combined. With the exception of the Harlow 1989 study that was restricted to borderline tumours, we have assumed that all studies included both borderline and invasive tumours, although this was not always clear in the publications.
3. RR or OR.
4. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
5. Estimated based on Table 1 of Gates 2010.
6. The Schildkraut 2016 case-control study presented two sets of results that both have some legitimacy for the present purpose. Schildkraut 2016A shows the results for all subjects who were interviewed in the study from 2010-2015. Schildkraut2016B shows the results for those subjects who were interviewed before 2014, and who, according to the authors, were not susceptible to having been tainted by publicity from a class action suit.

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Table 3. Main meta-analysis and sensitivity analyses conducted on the association between ever regular use of talcum powder products in the perineal area and ovarian cancer (all types combined).

Studies in meta-analysis	N*	RR-estimate			Heterogeneity	
		Meta-RR	95% CI	p-value	I ²	p-value
<i>Main Meta-Analysis - list in Figure 1 Forest plot</i>						
	21	1.28	1.19 1.38	0.00	32.9	0.07
<i>Sensitivity analyses</i>						
Substitute Gates 2008 for Gates 2010	21	1.30	1.21 1.40	0.00	22.9	0.16
Substitute Schildkraut B for Schildkraut A	21	1.27	1.17 1.37	0.00	30.8	0.08
Add Shushan	22	1.29	1.19 1.39	0.00	33.8	0.06
Substitute List A** for Terry	27	1.27	1.19 1.35	0.00	26.2	0.10
Substitute List A for Terry and Gates 2008 for Gates 2010	27	1.29	1.21 1.37	0.00	16.6	0.22
Substitute List A for Terry and Schildkraut B for Schildkraut A	27	1.26	1.18 1.34	0.00	24.5	0.12
Substitute List A for Terry and add Shushan	28	1.28	1.20 1.36	0.00	27.4	0.09

*N: Number of RRs that went into the meta-analysis. This is not synonymous with the number of studies because some RRs (e.g. Terry 2013, Cramer 2016) embody multiple studies.

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**List A studies: Cramer 2016; Wu 2015; Terry-Aus 2013; Terry-DOV 2013; Terry-Haw 2013; Terry-HOP 2013; Terry-NCO
2013; Terry SON 2013

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Table 4. Comparison of results of three contemporaneous and independent meta-analyses of the association between ever regular use of talcum powder products in the perineal area and ovarian cancer.

Meta-analysis author	N*	Meta-RR	95% CI	Heterogeneity p-value
Siemiatycki 2018	21	1.28	1.19-1.38	0.07
Berge 2018	27	1.22	1.13-1.30	0.02
Penninkilompi 2018	26	1.35	1.24-1.39	0.31

* Number of published RR estimates that went into the meta-analysis. This does not necessarily correspond to the number of studies, since, for example, the Terry 2013 pooled estimate used in the Siemiatycki meta-analysis embodied 10 studies.

Table 5. Relative risk estimates between ever regular use of talcum powder products on sanitary napkins and ovarian cancer, and results of meta-analysis.

Author	Number exposed cases	RR ¹	95% CI ²
Chang 1997	51	1.26	0.81 1.96
Cook 1997	38	0.9	0.5 1.5
Cramer 1999	20	1.45	0.68 3.09
Gertig 2000	32	0.89	0.61 1.28
Harlow 1989	8	2.6	0.9 22.4 ²
Harlow 1992	9	1.1	0.4 2.8
Houghton 2014	93	0.95	0.76 1.20
Ness 2000	77	1.6	1.1 2.3
Rosenblatt 1992	21	4.8	1.3 17.8
Rosenblatt 2011	55	0.82	0.58 1.16
Whittemore 1988	5	0.62	0.21 1.80
Wong 1999	13	0.9	0.4 2.0
Meta-analysis		1.08	0.89 1.31
p-value for heterogeneity = 0.09			

1. RR or OR.
2. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.

Table 6. Relative risk estimates between subgroups defined by cumulative exposure measures¹ and ovarian cancer², from various studies.

Author	Cumulative applications ³	Number exposed cases	RR ⁴	95% C.I.	
Cook 1997 ⁴	< 2000	20	1.8	0.9	3.5
	2001-5000	24	1.6	0.9	2.9
	5001-10000	21	1.2	0.6	2.4
	>10000	28	1.8	0.9	3.4
Harlow 1992	<1000	18	1.3	0.7	2.7
	1000-10000	54	1.5	0.9	2.4
	>10000	42	1.8	1.0	3.0
Mills 2004	Quartile 1	18	1.0	0.6	1.8
	Quartile 2	28	1.8	1.1	3.0
	Quartile 3	34	1.7	1.1	2.7
	Quartile 4	20	1.1	0.6	1.8
	10000+	18	0.87	0.48	1.57
Schildkraut 2016	≤3600	92	1.16	0.83	1.63
	>3600	152	1.67	1.23	2.26
Terry 2013 ⁵	Quartile 1	534	1.14	1.00	1.31
	Quartile 2	541	1.23	1.08	1.41
	Quartile 3	542	1.22	1.07	1.40
	Quartile 4	586	1.32	1.16	1.52

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a cumulative measure. All of these were case control studies.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. For the Cook study the metric was the number of days on which the woman had ever applied the powder. For the other studies the metric is based on an estimate of the total number of applications.

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4. RR or OR.

5. This study was based on a pooling of studies from 8 teams. Two of the teams (Cramer 2016 and Rosenblatt 2011) published separate analyses of risk by cumulative number of applications. But these are not shown here because they are rendered redundant by the Terry 2013 pooled results.

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Table 7. Relative risk estimates between subgroups defined by duration of use¹ and ovarian cancer², from various studies.

Author	Duration of use	Number exposed cases	RR ⁴	95% C.I.	
Chang 1997	<30	60	1.7	1.1	2.6
	30-40	71	1.4	1.0	2.2
	>40	41	0.9	0.5	1.4
Cramer 1999	<20 years	55	1.9	1.2	3.0
	20-30 years	32	1.3	0.8	2.3
	>30 years	59	1.4	0.9	2.3
Cramer 2016	< 8 years of use	133	1.31	1.03	1.68
	8-19 years of use	126	1.31	1.02	1.68
	20-35 years of use	147	1.35	1.07	1.70
	>35 years of use	129	1.33	1.03	1.71
Harlow 1992	<10 years	14	1.2	0.5	2.6
	10-29 years	49	1.6	1.0	2.7
	> 30 years	51	1.6	1.0	2.7
Houghton 2014	<9 years	135	1.09	0.88	1.36
	10+ years	97	1.02	0.80	1.30
Ness 2000	<1 year	17	2.0	1.0	4.0
	1-4 years	76	1.6	1.1	2.3
	5-9 years	40	1.1	0.8	1.9
	>10 years	233	1.2	1.0	1.5
Mills 2004	<3 years	18	1.0	0.6	1.8
	4-12 years	32	1.9	1.2	3.0
	13-30 years	29	1.5	0.9	2.3
	>30 years	21	1.2	0.7	2.1

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Author	Duration of use	Number exposed cases	RR ⁴	95% C.I.
Rosenblatt 2011	1-9 years	33	1.39	0.85 2.28
	10-19 years	29	1.46	0.87 2.45
	20-34 years	30	1.28	0.78 2.10
	35+ years	19	0.91	0.51 1.62
Schildkraut 2016	≤20 years	101	1.33	0.95 1.86
	>20 years	144	1.52	1.11 2.07
Whittemore 1988	1-9 years	34	1.6	1.0 2.6
	10+	50	1.1	0.7 1.7
Wong 1999	1-9 years	39	0.9	0.6 1.5
	10-19 years	49	1.4	0.9 2.2
	>20 years	101	0.9	0.6 1.2
Wu 2015	Per 5 years of exposure	1273	1.14	1.09 1.20

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of duration.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR.

Table 8. Relative risk estimates between subgroups defined by measures of frequency of use¹ and ovarian cancer², from various studies.

Author	Frequency of use	Number exposed cases	RR ⁴	95% C.I.	
Booth 1989	Rarely	6	0.9	0.3	2.4
	Monthly	7	0.7	0.3	1.8
	Weekly	57	2.0	1.3	3.4
	Daily	71	1.3	0.8	1.9
Chang 1997	<10 per month	76	1.8	1.2	2.7
	10-25 per month	54	1.1	0.7	1.7
	Per 10 applications per month		0.9	0.7	1.1
Cramer 1999	<30 per month	64	2.2	1.4	3.6
	30-39 per month	59	1.7	0.8	1.8
	≥40 per month	23	1.7	0.8	3.1
Cramer 2016	1-7 days per month	220	1.17	0.96	1.44
	8-29 days per month	110	1.37	1.05	1.78
	>30 days per month	205	1.46	1.20	1.78
Gates 2008	<1 per week	18	0.98	0.54	1.79
	1-6 per week	22	1.01	0.57	1.79
	Daily	35	1.44	0.88	2.37
Harlow 1992	<5 per month	32	1.5	0.8	2.7
	5-29 per month	24	1.2	0.6	2.2
	≥30 per month	58	1.8	1.1	3.0

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Author	Frequency of use	Number exposed cases	RR ⁴	95% C.I.
Mills 2004	<1 per week	34	1.3	0.9 2.1
	1-3 per week	31	1.6	0.7 1.8
	4-7 per week	41	1.7	1.1 2.6
Schildkraut 2016	<Daily	88	1.12	0.80 1.58
	Daily	158	1.71	1.26 2.33
Whittemore 1988	1-20 per month	41	1.3	0.8 2.0
	>20 per month	44	1.5	0.9 2.2

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of frequency of use.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR

Table 9. Relative risk estimates between ever regular use of talcum powder products¹ in the perineal area and invasive serous ovarian cancer, from various studies.

Author	Number exposed cases	RR ²	95% CI ³
Cook 1997	71	1.7	1.1 2.5
Gates 2010	131 ⁴	1.06	0.84 1.35
Harlow 1992	60	1.4	0.9 2.2
Houghton 2014	105	1.13	0.84 1.51
Mills 2004	42	1.77	1.12 2.81
Schildkraut 2016	165	1.38	1.03 1.85
Terry 2013	1197	1.24	1.13 1.35
Wong 1999	136	1.2	0.7 2.1
Meta-analysis		1.25	1.15 1.36

p-value for heterogeneity 0.06

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. RR or OR.
3. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
4. Estimated based on Table 1 of Gates 2010.

Table 10. Some major misconceptions in reviewing evidence on talc and ovarian cancer

1. Cohort studies are more valid and informative than case-control studies.
2. Hospital-based case-control studies are more valid and informative than the population-based case-control studies.
3. Counting the number of “statistically significant” results is a valid way of assessing the consistency of results among multiple studies.
4. If a product has been used for a long time, it must be safe
5. You cannot prove causality with an RR less than 2.0.
6. Government agencies provide a reliable up-to-date source of scientific information.
7. A biological mechanism must be proven before we can establish causality
8. Bradford-Hill “aspects” represent a recipe list of necessary ingredients.

Table 11. Selected examples of some of the recognized causal associations that have RR less than 2.0

Agent	Disease	Approximate RR
Urban air pollution	Lung cancer	1.09 ¹
Trichloroethylene	Kidney cancer	1.32 ²
Diesel engine emissions	Lung cancer	1.42 ³
Benzene	Leukemia	1.72 ⁴
Domestic radon gas	Lung cancer	1.29 ⁵
Second hand cigarette smoke	Lung cancer	1.64
Intermittent intense sun exposure	Melanoma of the skin	1.61 ⁶
Estrogen-progestin menopausal therapy	Breast cancer	1.59 ⁷

¹ Hamra GB, Guha N, Cohen A, et al (2014). Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis, *Environ Health Perspect* 122:906-911.

² Karami S, Lan Q, Rothman N, et al (2012). Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. *Occupational and Environmental Medicine* 69:858-867.

³ Mahjub H, Sadri G (2006). Meta-analysis of case-referent studies of specific environmental or occupational pollutants on lung cancer. *Indian Journal of Cancer* 43(4):169-173.

⁴ Khalade A, Jaakkola MS, Pukkala E, Jaakkola JJ (2010). Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environmental Health* 9(31):1-8.

⁵ Zhang Z-L, Sun J, Dong J-Y, et al (2012). Residential Radon and Lung Cancer Risk: An Updated Meta-analysis of Case-control Studies. *Asian Pac J Cancer Prev* 13:2459-2465.

⁶ Gandini S, Sera F, Cattaruzza MS, et al (2004). Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *European Journal of Cancer* 41:45-60.

⁷ Kim S, Ko Y, Lee HJ, Lim J (2018). Menopausal hormone therapy and the risk of breast cancer by histological type and race: a meta-analysis of randomized controlled trials and cohort studies. *Breast Cancer Research and Treatment* 170(3):667-675.

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Cigarette smoking	Cardiovascular disease	1.6 ⁸
Physically inactive (compared with physically active) ⁹	Hypertension	1.19
	Diabetes	1.12
Low fruit and vegetable diet	Cardiovascular disease	1.09 ¹⁰

⁸ Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on British male doctors, *British Medical Journal*, 328(7455):1519.

⁹ Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs, Jr DR, Liu K (2003). Cardiorespiratory Fitness in Young Adulthood and the Development of Cardiovascular Disease Risk Factors. *JAMA*, 290(23):3092-3100

¹⁰ Aune D, Giovannucci E, Boffetta P, Fadnes L, Keum N, Norat T, Greenwood D, Riboli E, Vatten L, Tonstad S (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies, *International Journal of Epidemiology* 43(3):1029-1056. (This RR estimate is computed from the reciprocal of the High fruit and vegetable variable that was reported by the authors. That is, 1/0.92).

Table 12. Bradford Hill aspects in relation to perineal talc exposure and ovarian cancer

Aspect	Brief comment	Weight in evaluating causality
Strength of the association	There are stronger associations and there are weaker associations	High
Dose response relationship	Reasonably clear increase in risk with increasing exposure	High
Consideration of alternative explanations – absence of bias	Yes considered, and none is compelling	High
Replication of the findings	Very strong, almost all studies support association	High
Temporal relationship	Exposure preceded disease in all studies	Moderate
Biological plausibility	There are plausible mechanisms	Moderate
Cessation of exposure	Not applicable.	Less
Specificity of the association	Yes, talc is not associated with a multitude of diseases	Less
Coherence with other knowledge	Could be similar to asbestos carcinogenicity	Less
Analogy		Less

12. Figures

Figure 1. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talc powder in the perineal area, based on all informative studies, studies ordered by magnitude of RR.

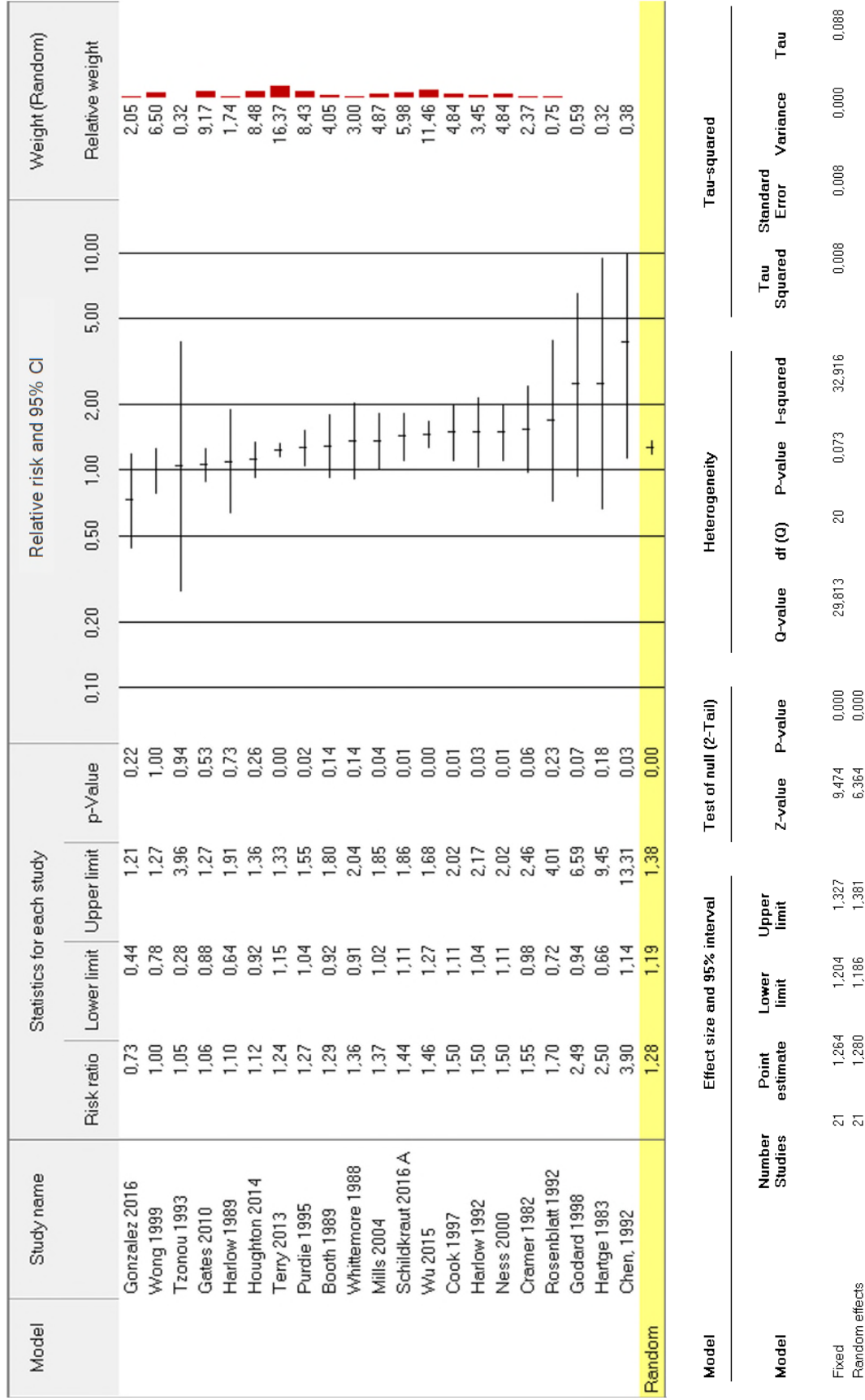
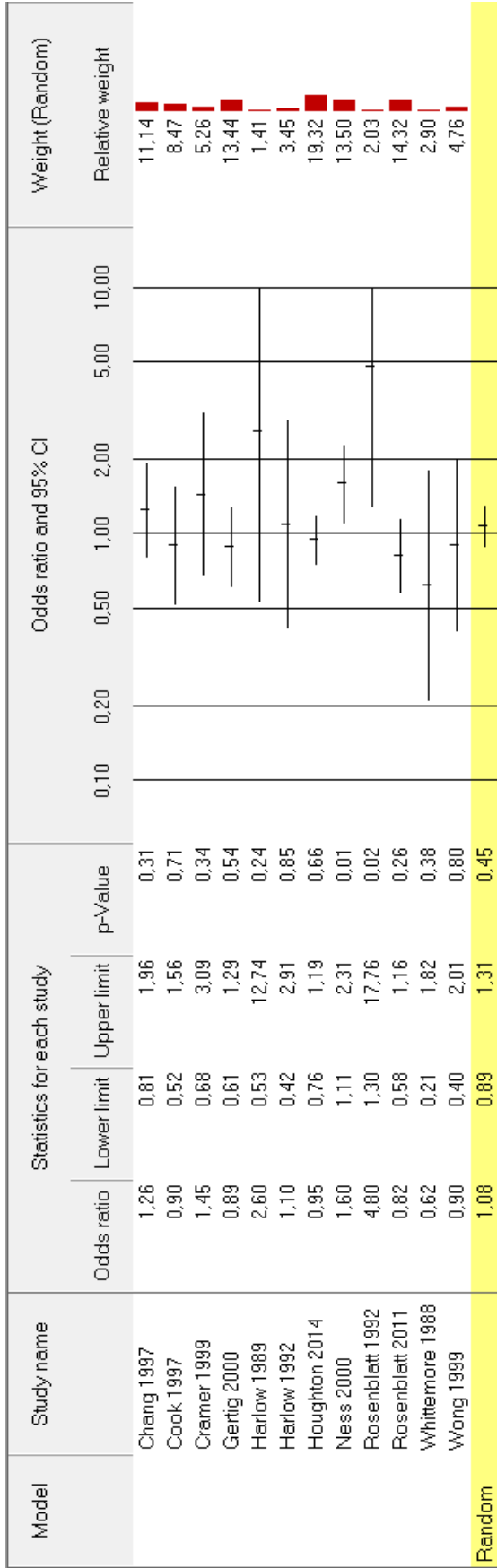
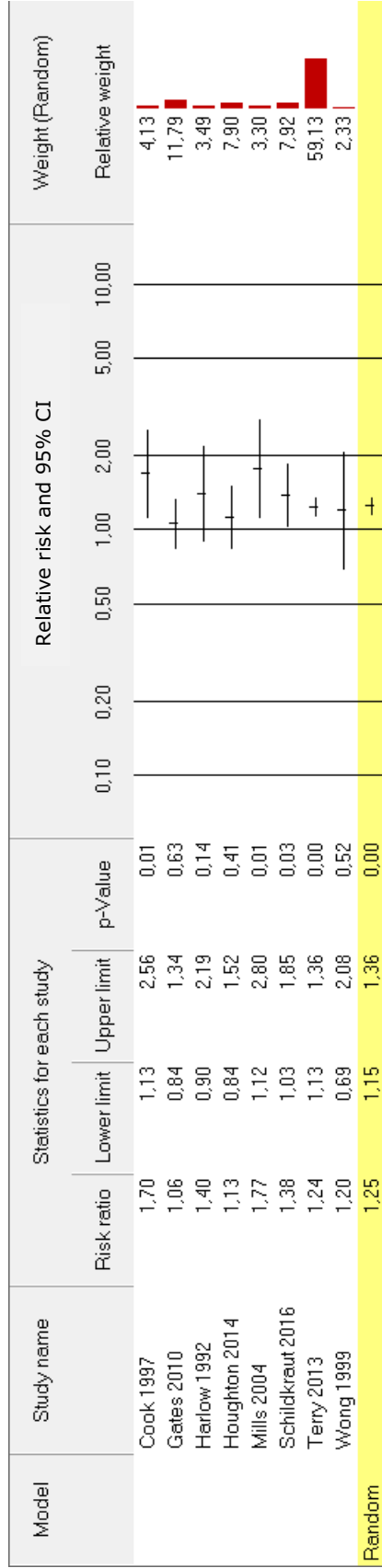


Figure 2. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talcum powder products on sanitary napkins, based on all informative studies.



Model	Effect size and 95% interval			Test of null (2-Tail)				Heterogeneity				Tau-squared		
	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (0)	P-value	I-squared	Tau Squared	Tau Standard Error	Variance	Tau
Fixed	12	1.041	0.911	1.189	0.591	0.554								
Random effects	12	1.078	0.888	1.309	0.763	0.445	17.614	11	0.091	37.551	0.037	0.045	0.002	0.193

Figure 3. Meta-analysis of relative risk of invasive serous ovarian cancer among women who regularly used talcum powder products in the perineal area, based on all informative studies



Model	Effect size and 95% interval			Test of null (2-Tail)			Heterogeneity			Tau-squared		
	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error
Fixed	8	1.250	1.161	1.345	5.963	0.000	7.401	7	0.388	5.422	0.001	0.011
Random effects	8	1.254	1.152	1.364	5.249	0.000					0.000	0.033

13. Appendix A

Appendix Table A1. Papers that contain some results on the association between exposure to perineal talc and ovarian cancer, and whether the paper was included in my meta-analyses of the binary Ever/Never exposed variable

Author	Included/excluded	Reasons for exclusion
Booth 1989	Core Inclusion	
Chang 1997	Core Inclusion	
Chen 1992	Core Inclusion	
Cook 1997	Core Inclusion	
Cramer 1982	Core Inclusion	
Cramer 1995	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 1999	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2005	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2016	Excluded when Terry 2013 is included	Considerable overlap between this and the Terry 2013 NEC component
Eltabbakh 1998	Excluded	Cases were peritoneal cancer and controls were ovarian cancer
Gates 2008 ²	Included in one sensitivity analysis	Overlap with Gates 2010

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Author	Included/excluded	Reasons for exclusion
Gates 2010 ²	Included in all analyses except one sensitivity analysis	This may be a more complete analysis than Gates 2008, but the degree of overlap is unclear.
Gertig 2000	Excluded	Subsumed in Gates 2008 and Gates 2010
Godard 1998	Core inclusion	
Gonzalez 2016	Core inclusion	
Green 1997	Excluded	This appears to be an analysis of a subset of the subjects in Purdie 1995
Hankinson 1993	Excluded	Numerical results were not presented.
Harlow 1989	Core inclusion	
Harlow 1992	Core inclusion	
Hartge 1983	Core inclusion	
Houghton 2014	Core inclusion	
Jordan 2007	Excluded	Benign tumours only
Kurta 2012	Excluded	Included in Terry 2013
Langseth 2004	Excluded	Not based on perineal application of cosmetic powder.
Lo-Ciganic 2012	Excluded	Same study as Kurta 2012 and included in Terry 2013.
Merrit 2008	Excluded	Included in Terry 2013

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Author	Included/excluded	Reasons for exclusion
Mills 2004	Core inclusion	
Moorman 2009	Excluded	Included in Terry 2013
Pike 2004	Excluded	Included in Terry 2013
Purdie 1995	Core inclusion	
Ness 2000	Core inclusion	
Rosenblatt 1992	Core inclusion	
Rosenblatt 2011	Core inclusion	
Schildkraut 2016	Core inclusion	
Shushan 1996	Included in sensitivity analysis	Unclear on how they obtained data on talc exposure or what the route of exposure was
Terry 2013	Included in Main analysis, but replaced by component studies in sensitivity analyses	
Tzonou 1983	Core inclusion	
Whittemore 1988	Core inclusion	
Wong 1999	Core inclusion	
Wu 2015	Core inclusion	

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Appendix Table A2. Some administrative and contextual information on the studies used in the following tables

Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Booth 1989	London, Oxford UK	1978-1983	Case-control; Hospital controls
Chen 1992	Beijing Cancer Registry	1984-1986	Case-control; Population controls
Cook 1997	Washington State	1986-1988	Case-control; Population controls
Cramer 1982	Boston	1978-1981	Case-control; Population controls
Cramer 2016	New England	1992-2008	Case-control; Population controls
Gates 2008 ²	USA – NHS study	1976-2004	Case-control nested in Cohort (US nurses)
Gates 2010 ²	USA – pooled 2 cohorts of nurses NHS and NHSII	1976-2004 1989-2005	Cohort (US Nurses)
Godard 1998	Montreal, Canada	1995-1996	Case-control; Population controls
Gonzalez 2016	Puerto Rico and 11 States USA	2003-2014	Cohort
Harlow 1989	Washington State	1980-1985	Case-control; Population controls
Harlow 1992	Boston	1984-1987	Case-control; Population controls

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Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Hartge 1983	Washington, DC	1974-77	Case-control; Population controls
Houghton 2014	USA	1993-2012	Cohort (WHI)
Mills 2004	California	2000-2001	Case-control; Population controls
Ness 2000	Pennsylvania, New Jersey, Delaware	1994-1998	Case-control; Population controls
Purdie 1995	Australia	1990-1993	Case-control; Population controls
Rosenblatt 1992	Baltimore	1981-1985	Case-control; Hospital controls
Schildkraut 2016	USA	2010-2015	Case-control; Population controls
Shushan 1996	Israel	1990-1993	Case-control Population controls
Terry 2013	Pooled 8 studies: USA & Australia	1984-2008	Case-control; Population controls
Terry-AUS 2013	Australia	2002-2006	Case-control Population controls
Terry – DOV ³ 2013	Washington State	2002-2009	Case-control Population controls
Terry – HAW 2013	Hawaii	1993-2008	Case-control Population controls

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Author	Study location	Years of case ascertainment/ follow-up¹	Type of study
Terry – HOP 2013	Pennsylvania, Ohio, Western NY State	2003-2008	Case-control Population controls
Terry – NCO 2013	North Carolina	1999-2008	Case-control Population controls
Terry – NEC 2013	Massachusetts, New Hampshire	1992-2006	Case-control Population controls
Terry – SON 2013	Southern Ontario	1989-1992	Case-control Population controls
Terry – USC 2013	Los Angeles County	1992-1998	Case-control Population controls
Tzonou 1983	Athens	1989-1991	Case-control; Controls – hospital visitors
Whittemore 1988	San Francisco	1983-1985	Case-control; Hospital & population controls
Wong 1999	Buffalo	1982-1992	Case-control; Hospital controls
Wu 2015	Los Angeles County	1992-2008	Case-control; Population controls

1. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
2. The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.
3. Terry – DOV 2013: the information in Terry 2013 is updated information included in Rosenblatt 2011.

Appendix Table A3. Covariates used in the analyses and exposure variables in the studies used in the following tables.

Author	Exposure variable selected	Covariates used in analysis
Booth 1989	At least monthly use	Since the authors did not present results for “ever” exposed, I calculated the OR from crude numbers in their tables. Therefore the OR presented is a crude one. However, results presented in Table 7 adjusted for age and social class
Chen 1992	Dusting perineum or lower abdomen > 3 months	Education
Cook 1997	Lifetime perineal application	Age
Cramer 1982	Any use as dusting powder and/or on sanitary napkins	Parity; menopausal status
Cramer 2016	Any talc use	Age; study center (MA, NH); BMI; primary relative with breast or ovarian cancer; parity; OC use; tubal ligation
Gates 2008 ¹	Regular genital talc use (1 per week or more)	Age; OC ² use; parity; BMI; post-menopausal hormone use
Gates 2010 ¹	Regular genital talc use (1 per week or more)	Age; BMI; physical activity; smoking; family history of breast or ovarian ca; OC use; tubal ligation; hysterectomy; age menopause; estrogen use
Godard 1998	Ever use of talc on perineum	Age; reproductive factors; OC use; tubal ligation; alcohol use; breast and abdominal surgery
Gonzalez 2016	Talc use in the past 12 months	Race; body mass index; parity; duration of oral contraceptive use; baseline menopause status; and patency

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Author	Exposure variable selected	Covariates used in analysis
Harlow 1989	Any genital talc use	Age; county; parity; OC use
Harlow 1992	Any genital talc use	Age; county; parity; marital status; education; religion; weight; use of sanitary napkins; douching
Hartge 1983	Any genital talc use	Race; age; gravidity
Houghton 2014	Combined use: longest duration of use among the applications to genitals, sanitary napkins and diaphragms	Age; race; OC use; HRT ³ use; family history of ovarian ca; age at last birth; BMI; smoking; tubal ligation; parity
Mills 2004	Ever use of talcum powder in genital area	Age; race/ethnicity; OC use; breast-feeding
Ness 2000	Genital rectal talc use	Age; parity; family history of ovarian ca;
Purdie 1995	Ever used talc in perineal region	Age; parity; duration of OC use; education; BMI; smoking; family history of ovarian ca
Rosenblatt 1992	Ever use of bath talc	Number of live births
Schildkraut 2016	Regular use of talc, cornstarch, baby or deodorising powder – at least once a month for 6 months	Age at diagnosis/interview; study site; education; tubal ligation; parity; BMI duration of OC use first degree family history of breast or ovarian cancer; and interview year
Shushan 1996	Talc use – never, seldom, moderate, a lot	Crude OR

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Author	Exposure variable selected	Covariates used in analysis
Terry 2013 – all components of the pooled analysis	Genital powder use	Age; OC use; parity; BMI; tubal ligation; ethnicity; race; tubal ligation; hysterectomy; breastfeeding
Tzonou 1983	Ever use of talc in perineal region	Age; years of schooling; weight before onset of the disease; age at menarche; menopausal status and age at menopause; parity and age at first birth; tobacco smoking; coffee drinking; consumption of alcoholic beverages; hair dyeing; use of analgesics and tranquilizers/hypnotics
Whittemore 1988	Talcum powder used on any two of perineum, sanitary pads and diaphragm	Age; race; hospital; parity
Wong 1999	Ever use of talc on genital region or thighs	Age; income; education; geographic location; OC use; smoking; family history of ovarian ca; age at menarche; menopausal status; tubal ligation or hysterectomy
Wu 2015	Genital talc use >1 year	Age; race/ethnicity; interviewer; reproductive variables; sociodemographic variables; medical history; hormonal variables; BMI.

1. The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.
2. OC: oral contraceptive
3. HRT: hormone replacement therapy

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14. Appendix B

Comparison of studies used and results extracted from articles referenced in three different meta-analyses.*

Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
Booth 1989 1.30 (0.94-1.80)	Booth 1989 1.29 (0.92 - 1.80)	Booth 1989 1.29 (0.92 - 1.80)
Chang 1997 1.42 (1.08 – 1.86)	Chang 1997 1.35 (1.03 - 1.76)	
Chen, 1992 3.90 (1.43 – 10.60)	Chen, 1992 3.90 (0.91 - 10.60)	Chen, 1992 3.90 (0.91 - 10.60)
Cook 1997 1.50 (1.11 – 2.02)	Cook 1997 1.50 (1.10 - 2.00)	Cook 1997 1.50 (1.10 - 2.00)
Cramer 1982 1.60 (1.21 – 2.12)	Cramer 1982 1.92 (1.27 - 2.89)	Cramer 1982 1.92 (1.27 - 2.89)
Cramer 2016 1.42 (1.03 – 1.95)	Cramer 2016 1.32 (1.14 - 1.50)	Cramer 2016 1.33 (1.16 – 1.52)
		Gates 2008 1.24 (0.83 - 1.83)
	Gates 2010 1.06 (0.89 - 1.28)	Gates 2010 1.06 (0.89 - 1.28)
Gertig 2000 1.09 (0.86 – 1.38)		

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Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
<i>Godard 1998</i> 2.49 (0.94 - 6.58)	<i>Godard 1998</i> 2.49 (0.94 - 6.58)	<i>Godard 1998</i> 2.49 (0.94 - 6.58)
<i>Gonzalez 2016</i> 0.73 (0.44 - 1.20)	<i>Gonzalez 2016</i> 0.73 (0.44 - 1.20)	<i>Gonzalez 2016</i> 0.73 (0.44 - 1.20)
Green 1997 1.30 (1.06 - 1.60)	Goodman 2008 0.99 (0.7 - 1.41)	
Harlow 1989 1.10 (0.58 - 2.10)	<i>Harlow 1989</i> 1.10 (0.70 - 2.10)	<i>Harlow 1989</i> 1.10 (0.70 - 2.10)
<i>Hartge 1983</i> 2.50 (0.66 - 9.45)	<i>Harlow 1992</i> 1.50 (1.00 - 2.10)	<i>Harlow 1992</i> 1.50 (1.00 - 2.10)
<i>Houghton 2014</i> 1.12 (0.92 - 1.36)	<i>Hartge 1983</i> 2.50 (0.70 - 10.00)	Hartge 1983 0.70 (0.40 - 1.10)
Kurta 2012 1.40 (1.16 - 1.69)	Houghton 2014 1.06 (0.87 - 1.28)	<i>Houghton 2014</i> 1.12 (0.92 - 1.36)
	Lo-Ciganic 2012 1.34 (1.07 - 1.66)	

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Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
Merritt 2008 1.17 (1.01 - 1.36)	Merritt 2008 1.13 (0.92 - 1.38)	
Mills 2004 1.37 (1.02 - 1.85)	Mills 2004 1.37 (1.02 - 1.85)	Mills 2004 1.37 (1.02 - 1.85)
	Moorman 2009 1.37 (1.05 - 1.8)	
Ness 2000 1.50 (1.10 - 2.02)	Ness 2000 1.50 (1.10 - 2.00)	Ness 2000 1.50 (1.10 - 2.00)
Purdie 1995 1.27 (1.04 - 1.54)	Purdie 1995 1.27 (1.04 - 1.54)	Purdie 1995 1.27 (1.04 - 1.54)
Rosenblatt 1992 1.70 (0.72 - 4.01)	Rosenblatt 1992 1.70 (0.70 - 3.90)	Rosenblatt 1992 1.70 (0.70 - 3.90)
Rosenblatt 2011 1.27 (0.97 - 1.66)	Rosenblatt 2011 1.13 (0.93 - 1.36)	
Schildkraut 2016 1.44 (1.11 - 1.86)	Schildkraut 2016 1.44 (1.11 - 1.86)	Schildkraut 2016 A 1.44 (1.11 - 1.86)
		Schildkraut 2016 B 1.19 (0.87 - 1.63)
Shushan 1996 2.00 (1.11 - 3.60)		Shushan 1996 1.97 (1.06 - 3.66)

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Penninkilampi 2018	Berge 2018	Siemiatycki 2018
Study / RR(95%CI)	Study / RR(95%CI)	Study / RR(95%CI)
<i>Tzonou 1993</i> 1.05 (0.28 - 3.96)	<i>Tzonou 1993</i> 1.05 (0.28 - 3.98)	Terry 2013 1.24 (1.15 - 1.33)
Whittemore 1988 1.40 (0.98 - 2.00)	<i>Whittemore 1988</i> 1.36 (0.91 - 2.04)	<i>Tzonou 1993</i> 1.05 (0.28 - 3.98)
Wong 1999 0.92 (0.24 - 3.57)	<i>Wong 1999</i> 1.00 (0.80 - 1.30)	<i>Whittemore 1988</i> 1.36 (0.91 - 2.04)
Wu 2015 1.32 (1.14 - 1.52)	<i>Wu 2015</i> 1.46 (1.27 - 1.69)	<i>Wong 1999</i> 1.00 (0.80 - 1.30)
		<i>Wu 2015</i> 1.46 (1.27 - 1.69)

* When two or three of the meta-analyses extracted the identical results from the source paper, it is indicated with italic characters.

15. Appendix C

Examples of historic discoveries made on the basis of empirical observation of an association, without the existence of a validated biological mechanism of action.

- Jenner (18th century) discovered that smallpox could be prevented by “vaccinating” people. This was based on observation of the effect of exposure to cowpox. He had no idea about viruses or the biology of smallpox. He only knew that the “association” he observed between vaccination and the prevention of smallpox was so strong as to convince him it was causal. Millions of lives were saved as a result.
- Snow (19th century) discovered that cholera was caused by something in the water supply. He did not know what the pathogen was or how it produced the disease, but he showed with sufficient epidemiologic proof that drinking water from a polluted source produced much higher rates than drinking water from a clean source. Despite the ignorance of biological mechanisms, the public health authorities acted on his findings and thereby greatly reduced the incidence of cholera.
- Rheumatic fever and rheumatic heart disease were quite common causes of disease and death, striking relatively young people. For many decades it was recognized that there was an association between infection with the streptococcus bacterium and rheumatic heart disease, but it was not understood how the bacterium could have such an effect. The lack of understanding of the biological mechanisms did not get in the way of prevention of rheumatic heart disease by preventing and treating streptococcus infection.
- In the 1930’s and 1940’s, it was noticed that communities with high natural levels of fluoride in the water had much lower levels of dental caries than communities with low fluoride levels. Additional observational research confirmed the clear causal relationship and this led to extensive use of fluoride in various ways to reduce dental disease. But, all this occurred

before the mechanisms by which fluoride acted on teeth were understood. And, indeed the mechanisms are still not fully understood.

- In the late 1940's and early 1950's, evidence was accumulating that cigarette smokers had higher rates of lung cancer than non-smokers. This "association" was ridiculed at the time, among other reasons, because there was no proven biological mechanism. Attempts to replicate smoking-related lung cancer incidence in laboratory animals were largely unsuccessful. Nor was there a deep understanding of the cellular processes that allow the inhalation of cigarette smoke to culminate in a tumor. Scores of studies later and many decades later, the outlines of a credible biological mechanism began to emerge. The absence of a proven biological mechanism did not hinder the US Surgeon General and other national bodies from concluding that there was a causal link as early as the 1960's.

- Many chemicals have been found to be carcinogenic as a result of epidemiologic studies among workers. Examples of these are asbestos, silica, nickel compounds, chromium compounds, benzene, and others. Some of these discoveries go back to the first half of the 20th century, and, for most of them, many decades passed between the time they were recognized as carcinogens, on the basis of epidemiologic associations, and the elaboration of credible mechanisms of how they induce cancer. (Siemiatycki 2015) Most known carcinogens were first discovered empirically by medical doctors or epidemiologists, usually as part of large data collection activities or just plain astute observation on the part of medical doctors.

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Agenda: NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee
Meeting

Annie Yessian Report - Echeverria

Berg v. Johnson & Johnson, Final Jury Instructions

Berg v. Johnson & Johnson, Judgment

Berg v. Johnson & Johnson, Verdict Form October 4, 2013

California State Cosmetics Program from the California Dept of Public Health - Occupational
health Branch - Chemicals known or suspected to cause cancer or reproductive
toxicity (P-31)

California Safe Cosmetics Act 2005

Carl v. J&J; Balderrama v. J&J - Defendants Johnson & Johnson, Johnson & Johnson Consumer Inc., and Imerys Talc America, Inc's joint memorandum of law in support of their motion to exclude plaintiffs' experts' general causation opinions

Cancer Prevention Coalition – November 17, 1994 Citizen's Petition to FDA seeking carcinogenic labelling on all cosmetic talc products

Cancer Prevention Coalition – May 13, 2008 Citizen's Petition to FDA seeking a cancer warning on cosmetic talc products

Cesario, S - Powerpoint "Feminine hygiene product use and the risk of ovarian cancer"

Committee on the State of the Science in Ovarian Cancer Research; Board on Health Care Services; Institute of Medicine; National Academies of Sciences, Engineering, and Medicine. Ovarian Cancers: Evolving Paradigms in Research and Care

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Crowley M. (November 12, 2018) Rule 26 report of Michael M. Crowley, PhD regarding the fragrance chemical constituents in Johnson & Johnson Talcum Powder Products

Daniel Cramer Report - Echeverria

Daniel Cramer Supplemental Report - Echeverria

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David Steinberg signed verification Di Saia, P. J. (2015). Letter to Kathleen A. Frazier. Unpublished letter.

Defense Expert Reports from Blaes Case: DeSesso; Hoel; Di Saia; Muscat; Hopkins

Deposition Exhibit of John Hopkins – 28 (November 5, 2018)

Deposition Exhibit of Julie Pier – 47 (September 13, 2018)

Deposition Transcript of Alice Blount, *Ingham v. Johnson & Johnson, et al.* (April 13, 2018)

Deposition Transcript & Exhibits - Julie Pier, MDL No. 2738 (September 12 – 13, 2018)

Deposition transcript, 10/19/2012 - John Hopkins

Deposition Transcript & Exhibits - John Hopkins, MDL No. 2738 (Aug. 16 – 17, 2018, Oct. 17, 2018, Nov. 5, 2018)

Deposition Transcript & Exhibits - Joshua Muscat, MDL No. 2738 (Sept. 25, 2018)

Deposition Transcript & Exhibits - Linda Loretz, MDL No. 2738 (July 17, 2018, Oct. 1 – 2, 2018)

Deposition Transcript & Exhibits - Robert Glenn, MDL No. 2738 (Oct. 18, 2018)

D. L. Longo, R. C. Young. Cosmetic talc and ovarian cancer (1979)

D. L. Longo, R. C. Young. Letter to the Editor: Cosmetic talc and ovarian cancer (1979)

Educational Report of Thomas Dydek

Excerpts from S. Sharma Deposition

Expert Report of Laura M. Plunkett, PhD, DABT – Oct. 5, 2016

Expert Report of Jack Siemiatycki, MSc, PhD – Oct. 4, 2016

Fair warning TalcDoc 5 - Exhibit 113 (JNJNL91_000022019)

Fair warning TalcDoc 15

FDA Authority Over Cosmetics April 6, 2015

FDA Response to Citizen's Petition re: Docket Numbers 94P-0420 and FDA-2008-P-0309-00001/CP

Federal Register – 81 FR 91722 – Banned Devices – Powdered Gloves

Fox v. Johnson & Johnson, Trial Transcript

Godleski, J. J. (2015). Letter to R. Allen Smith, Jr. Unpublished letter.

John J. Godleski, M.D. - Expert Report from Blaes Case

John Godleski Report - Echeverria

John Godleski Supplemental Report - Echeverria

Hopkins, J. (2015). Letter to Gene M. Williams. Unpublished letter.

Johnson's Baby Powder - website, product description

Kemp Hearing Transcript - Douglas Weed

Longo, Rigler, Egeland. MAS Project 14-1852: Below the Waist Application of Johnson & Johnson Baby Powder, September 2017

Longo, Rigler - Analysis of Johnson & Johnson Baby Powder & Valiant Shower to Shower talc products for amphibole (tremolite) asbestos, August 2017

Longo, Rigler - Analysis Report MAS Project #14-1683 Johnson's Baby Powder Sample Set, April 2017

Longo, Rigler - TEM Analysis of historical 1978 Johnson's Baby Powder Sample for amphibole asbestos, February 2018

Longo, Rigler – Expert Report In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (November 14, 2018).

“Making it up as he goes along: Paolo Boffetta, Italian Epidemiologist, distorts power line health risks” - <https://microwavenews.com/news-center/boffetta-post-truth>.

Material Safety Data Sheet from Luzenac America, Inc.; Version 45.0, updated 6/18/08 (Group 1)

Material Safety Data Sheet from Luzenac America, Inc. (Group 3)

Material Safety Data Sheet from Luzenac America, Inc.; Version 2.0, updated 2/26/09 (Group CAN)

Material Safety Data Sheet from Luzenac America, Inc. (Group 1)

MBS Invoices – December 2007, April 2012, May 2013, July 2013, December 20013, January 2015, March 2015

MSDS Sheet, Version 2.0

Muscat, J. E. (2015). Report on the Relationship between Hygienic Use of Talc and the Risk of Ovarian Cancer. Unpublished report.

NPR Article Johnson & Johnson Pledges to Purge Controversial Chemicals April 16, 2015

Ness, R. B. (2015). Report on the question of whether genital talc use causes ovarian cancer. Unpublished report.

Ness, R. Expert Report - Jacqueline Fox

Ness, R. Commentary "A plaintiff's witness in the baby powder case"

NTP "The Report on Carcinogens Tenth Edition - Factsheet"

Omiecinski, C. J. (2015). Opinion on the Relationship Between Chronic Perineal/Genital Exposures to Cosmetic Talc and Ovarian Cancers: Mechanistic Aspects and Biological Plausibility Unpublished report.

Osann, K. (2016). Report on Perineal Talc Exposure and Risk of Ovarian Cancer. Unpublished report.

Personal Care Products Council Letter – July 21, 2009 to FDA re: Comments to FDA Citizen's Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products

Photographs of Johnson's Baby Powder

Photographs of Shower to Shower

Riham Sheble, Shabina Khatri. DOHA News - Johnson's baby powder of Qatar shelves after US cancer lawsuit verdict

Roe. Controversy: Cosmetic talc and ovarian cancer (1979)

Rosenthal, G. J. (2015). Opinion on Relationships Between the Toxicology of Cosmetic Talc and the Pathogenesis of Ovarian Cancer. Unpublished report.

Rosenthal, G - Expert Report from Blaes Case: "Opinion on Relationships Between the Toxicology of Cosmetic Talc and the Pathogenesis of Ovarian Cancer"

Rothman, Pastides, Samet. (2000) Interpretation of epidemiologic studies on talc and ovarian cancer

Slemp v. Johnson & Johnson, et al., Trial Transcript

Summary Minutes of the NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meeting

Talc Removed from 12th RoC- The Rose Sheet October 24, 2005

WHMIS Classification for Talc, non fibrous - CNESST; CAS Number: 14807-96-6

Weed, Douglas. A Report Regarding General Causation and an Evaluation of the Reliability and Validity of the Plaintiffs' Experts' Reports Designated for the Plaintiff, Lori Oules (Feb. 1, 2017)

17. Curriculum Vitae – Jack Siemiatycki

CURRICULUM VITAE

Jack Siemiatycki

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STATISTICAL SUMMARY OF SELECTED ACCOMPLISHMENTS

Publications in peer-reviewed journals	245
Book chapters, IARC Monographs	20
Other publications, reports	42
Book (authored)	1
Invited presentations	173
Conference presentations, posters, abstracts : offered and accepted	181
Grants received as P.I. (number)	36
Grants received as P.I. (\$)	\$15.4M
Grants received as co-investigator (number)	59
Grants received as co-investigator (\$)	\$27.9M
H-factor (google scholar)	64
Instances of participation on expert panels, committees, boards of directors, at invitation of governments or public health agencies or research agencies or universities	126
Grant review panels or referee for external institution or journal editorial boards	65
Honours	several

GENERAL INFORMATION

Work address

Université de Montréal
Research Center of CHUM
850 rue St Denis, Montréal, QC, Canada H2W 1V1

Tel: (514) 890-8166
Fax: (514) 412-7106
E-mail: j.siemiatycki@uMontréal.ca

EDUCATION

1967 B.Sc. (mathematics); McGill University
1970 M.Sc. (mathematical statistics); McGill University
1976 Ph.D. (epidemiology and medical statistics); McGill University
1977 Post-doctoral (cancer epidemiology); International Agency for Research on Cancer, Lyon

CURRENT ACADEMIC APPOINTMENTS

Professor, Department of Social and Preventive Medicine, Université de Montréal (since 2001)
Cancer Research Society-Guzzo Research Chair in Environment and Cancer, Université de Montréal (since November 2007)
Adjunct Professor, Department of Epidemiology, Biostatistics and Occupational Health, McGill University. (since 1979)
Fellow, Canadian Academy of Health Sciences (since 2008)

PREVIOUS ACADEMIC APPOINTMENTS AND WORK EXPERIENCE

1967-71 Research Fellow; Department of Epidemiology and Health, McGill University.
1970-72 Research Director; Pointe St. Charles Community Clinic, Montréal.
1978 Consultant; International Agency for Research on Cancer, Lyon.
1978-2001 Assistant, then Associate (1979), then full Professor (1983):
Epidemiology Research Center, Institut Armand-Frappier, Laval, Québec.
1982-1986 Associate member, McGill Cancer Center, McGill University.
1996-1997 Visiting Scientist. International Agency for Research on Cancer, Lyon.
2001-2015 Canada Research Chair (Tier 1), Université de Montréal (resigned 2011).
2003-2009 Affiliate Scientist. McLaughlin Centre for Pop'n Health Risk Assessment, Univ of Ottawa.

SIGNIFICANT INTERNAL ADMINISTRATIVE APPOINTMENTS

1982-86 Director, Équipe associée de l'Institut de Recherche en Santé et Sécurité du Travail sur les cancers professionnels (affiliated research team of the Quebec Institute for Occupational Health and Safety on Occupational Cancer).
1988-91 Director, Epidemiology Research Center, Institut Armand-Frappier.
1990-98 Director, Équipe prioritaire de recherche en épidémiologie environnementale du FRSQ. (Priority research team in environmental epidemiology)
1998-2001 Member, Governing Council (Conseil d'administration). Institut national de la recherche scientifique, Université du Québec.
2000-2007 Coordinator. Program of Research in Environmental Epidemiology of Cancer (PREECAN), a national program funded by the National Cancer Institute of Canada.
2002-2005 Associate Director for Population Health Sciences, Research Center of the University of Montréal Hospital Center.

2006-2007 Director, Epidemiology program, PhD public health, Université de Montréal.
2006-2014 Director, Axe risques à la santé (Health Risks Division). Centre de recherche du Centre hospitalier de l'Université de Montréal.

SIGNIFICANT INSTITUTIONAL COMMITTEES

1979-80 Member of faculty committee to negotiate a collective agreement with the Institut Armand-Frappier administration.
1982-92 Member, Research Council. Institut Armand-Frappier.
1998-2001 Member, Institutional advisory council. Institut Armand-Frappier. Institut national de la recherche scientifique
2002-2006 Comité de direction. Centre de recherche du CHUM
2002-2017 Member, Various committees of the Dept Med Soc et Preventive, including Promotions, and Recruitment.
2006-2009 Member, Various committees established to set up a new School of Public Health at l'Université de Montréal
2006-2014 Comité Scientifique de la Recherche du CHUM.

CURRENT MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES (INVITED)

1. Chair of Scientific Advisory Committee of CONSTANCES, a large prospective cohort established in France, under aegis of INSERM, Ministère de la Santé, and other agencies. Since 2011.
2. Member of Comité national d'épidémiologie en cancérologie. Ministère de la Santé et des Services sociaux, Quebec. Since 2014.
3. Member, Advisory committee to Directors of Cartagene, a Quebec population cohort.

PAST MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES, CONSULTATIONS (INVITED)

1. Expert consultative committee to Commission de la santé et sécurité du travail du Québec on the epidemiologic function of the CSST. 1979-80.
2. President of Organizing Committee of Annual Congress of Quebec Public Health Association, Montréal. 1982.
3. Consultative committee of International Agency for Research on Cancer on feasibility of SEARCH programme. 1982.
4. Canadian representative. International Joint Commission (U.S. and Canada) Committee on the Assessment of Human Health Effects of Great Lakes Water Quality. 1982-89.
5. Task Force on Chemicals in the Environment and Human Reproduction Effects in New Brunswick. 1983-85.
6. Chairman and organizer of international workshop sponsored by International Agency for Research on Cancer, Lyon, on use of job exposure information in cancer case-control studies. 1984.
7. Quebec Government Consultative Committee on Alachlor. 1985-86.
8. Chairman and organizer of the International Joint Commission Workshop on the Role of Epidemiology in Assessing the Effects of Great Lakes Water Quality on Human Health, Scarborough, March 1988. 1986-88.
9. Priority Substances Advisory Panel. Panel established under terms of Canadian Environmental Protection Act by Health and Welfare Canada. 1988.
10. Working Group on Electromagnetic Fields under auspices of Health Effects Institute. 1991.
11. Consultative Committee on Environment-related Cancer Surveillance, LCDC, Health and Welfare Canada. 1993-1996.
12. Consultative Committee on an Investigation of Lung Cancer and Environmental Tobacco Smoke, Environmental Health Directorate, Health Canada. 1994-1995.
13. Working Group on Evaluation of Carcinogenicity of Carbon Black, Printing Trades and Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 1995.

14. Working Group on Human Cancer Risks associated with Chrysotile Asbestos. World Health Organization (IPCS) Geneva, June 1995.
15. Secretariat on Evaluation of Chemopreventive Effect of Aspirin and Other NSAIDS for Cancer. International Agency for Res. on Cancer, Lyon, Apr. 1997.
16. Chair. Symposium on Health Risks of Water Disinfection By-products. Convened by Health Canada. Ottawa. May 1997.
17. Working Group. Meeting on Species-specificity in response to carcinogens. Monograph Programme. International Agency for Res. on Cancer, Lyon, Nov. 1997.
18. Board of Directors. Canadian Society for Epidemiology and Biostatistics. 1997-1999.
19. Working Group. Evaluation of Carcinogenicity of Various Industrial Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, Feb. 1998.
20. Canadian Coalition on Cancer Surveillance. 1997-2002.
21. External site review panel. U.S. National Cancer Institute Epidemiology Branch. June 1999.
22. Organizing Committee for Medical Research Council Workshop on Privacy of Health Data. 1999-2000.
23. Organizing Committee, EPI2001. Joint North American Congress of Canadian Society for Epidemiology and Biostatistics, Society for Epidemiologic Research, American Public Health Association (Epid) and American College of Epidemiology, Toronto, 14 – 16 June 2001. 1999-2001.
24. Coordinator of national initiative of the public health community to provide guidance on the structures and functioning of the new Canadian Institutes of Health Research. 1999-2000.
25. Organizing Committee. World Congress of the International Epidemiological Association, Montréal, 18-22 August 2002. 2001-2002.
26. President. Canadian Society for Epidemiology and Biostatistics. 2001-2003. Member of Board. 1997-1999.
27. Working Group. Evaluation of Carcinogenicity of Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 2003.
28. Jury of Consensus Conference on risks and benefits of vaccination for hepatitis B. For Minister of Health of France. Organized by INSERM and ANAES. Paris 2003.
29. Public Advisory Panel. Vinyl Council of Canada. 1998-2004.
30. Advisory Panel. U.S. National Cancer Institute Brain Tumor Study. 1998-2003.
31. Scientific Advisory Committee. Boeing/UAW Workers' Health Studies. 1999-2005.
32. Institute Advisory Board. Canadian Institutes for Health Research – Institute of Circulatory and Respiratory Health. 2001-2005.
33. National Occupational Research Agenda (NORA). Joint consultative committee for US National Cancer Institute and US National Institute for Occupational Safety and Health. 2002-2005.
34. Canadian Cancer Surveillance Alliance. Consultative committee of Health Canada, Canadian Cancer Society, Provincial Cancer Registries, Statistics Canada. 2002-2003.
35. Co-president. Organizing Committee of Joint SER-CSEB Congress, Toronto 27-30 June 2005. (2004-2005).
36. Chair. Monograph Program Meeting. International Agency for Research on Cancer (WHO), France. February 2006.
37. Advisory Committee on Research Ethics and Databanks. Quebec Health Research Council (FRSQ). 2003-2011.
38. Board of Directors. American College of Epidemiology. 2003-2006.
39. Board of Directors. National Cancer Institute of Canada. 2003-2007.
40. Member Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2005-2009.
41. Elected Chair. Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2008-2009.
42. Scientific Advisory Council Canadian Partnership Against Cancer 2007-2009.
43. Advisory Committee. Occupational Cancer Research Centre of Ontario. Since 2009.
44. Working Group on Cancer Prevention, CPAC, 2007-2010.

45. Subgroup Chair and Working Group Member. Evaluation of Carcinogenicity of Non-Ionizing Radiation, Radiofrequency Electromagnetic Fields. Monograph Programme. International Agency for Research on Cancer, Lyon May 2011.
46. Member of Scientific Advisory Board of Bordeaux cancer research center SIRIC-BRIO, Bordeaux France. Since 2013.
47. Member of external review panel. Helmholtz Center Munich Research Institute. Germany. July 2011.
48. Conseil Scientifique de l'Institut de Recherche en Santé Publique (IReSP). Under aegis of INSERM and Ministère de la Santé, France. 2004-2009.
49. Adviser and expert witness for legal team conducting a major class action lawsuit against the Canadian tobacco industry. 2007-2014.

OTHER SIGNIFICANT EXTERNAL CONSULTATIONS (INVITED)

1. Consultation with Quebec Ministry of Justice regarding compensation for homeowners who were advised to use formaldehyde-base home insulation - 1983.
2. Invited participant. Workshop convened by the Science Council of Canada on the future of Epidemiology in Canada, Ottawa - 1985.
3. Consultation with Government of Alberta regarding the evaluation of a report alleging significant health impact in the environment of a sour-gas plant - 1985.
4. Consultation with Quebec Ministry of Environment regarding health effects of residency near an abandoned toxic waste site in LaSalle, Quebec - 1987.
5. Invited participant. Workshop convened by Canadian Public Health Association, Environment Canada and Health and Welfare Canada on Environmental Impact Assessment, Ottawa - 1987.
6. Invited participant. Annual workshops convened by Health Protection Branch of Health and Welfare Canada to discuss the role of Canada in the SEARCH programme of the International Agency for Research on Cancer, Ottawa - 1987-1989.
7. Consultation with Quebec Cree Band Council regarding a research proposal to study developmental effects of consuming fish with high mercury levels - 1989.
8. Invited participant. Workshop convened by Ontario Industrial Disease Standards Panel on the use of epidemiologic data in workers' compensation, Toronto - December 1989.
9. Invited participant. Workshop convened by National Academy of Sciences (U.S.) on Carcinogenicity of Complex Mixtures, Tucson, Arizona - Jan 1990.
10. Invited participant. Workshop convened by Laboratory Centers for Disease Control, Health and Welfare Canada on Multiple Chemical Sensitivities, Ottawa - May 1990
11. Member of expert advisory panel to the pan-Canadian case-control study of electromagnetic fields and childhood leukemia. Sponsored by Canadian Electrical Assoc, EPRI (U.S.A.), Health and Welfare Canada. 1990-1996.
12. Organizer of Workshop to Plan a Pan-North American Case-control Study of Lung Cancer. Sponsored by Health and Welfare Canada. Toronto. March 1991.
13. Invited participant. Workshop convened by Environmental Health Directorate of Health and Welfare Canada, on Environmental Epidemiology in Canada. Ottawa. March 1992
14. Invited participant. Workshop convened by Harvard Center for Risk Analysis on implementing a new type of risk assessment. Maryland. April 1992.
15. Member of Technical Advisory Panel for epidemiology studies of foundry workers - CIIT. Research Triangle Park, N.C. Feb. 1993
16. Consultant to Health Effects Institute - Asbestos Research, on Options for Characterizing Worker Activities in Buildings, Boston. Feb. 1993.
17. Advisory panel to Laboratory Centers for Disease Control, Health and Welfare Canada, on Environmental Epidemiology under the Green Plan. March 1993.
18. Member of External Advisory Committee. Champlain Adirondack Biosphere Environmental Health Sciences Center, University of Vermont. 1993.
19. Consultant to Michigan Cancer Foundation on a variety of epidemiologic studies. 1993-1996.

20. Invited to address President Clinton's Panel on Cancer regarding priorities in cancer research. Bethesda, MD. April 1994.
21. Invited participant. Science and Technology Review Consultation. Government of Canada. Montréal. September 1994.
22. Invited participant. Strategic planning workshop to reduce Environmental Tobacco Smoking exposure. Laboratory Centre for Disease Control. Health Canada. Oct 1995.
23. Invited participant. Meeting to establish new priorities for funding. National Health Research and Development Programme of Canada. Montréal. Feb 1996.
24. Chair Scientific Advisory Committee for the Dalhousie University study of health effects of environmental and occupational pollution in the area of the Sydney, Nova Scotia steel industry. 1996.
25. Member of two Ministerial missions of the Quebec and Canadian governments to France to discuss with French experts the risks associated with low level exposure to chrysotile asbestos. Paris. Oct 1996.
26. Chair. Meeting of collaborators of European network of studies on lung cancer and smoking.
27. International Agency for Res. on Cancer, Lyon. June 1997.
28. Member of Canadian scientific delegation to United Kingdom to discuss with British experts the risk associated with low level exposure to chrysotile asbestos. London, Sept. 1997.
29. Symposium chair. Workshop to discuss methods of predicting numbers of cases of mesothelioma to be expected in various countries. Paris. Dec. 1997.
30. Invited participant and subgroup reporter. Peer Review on Hazard Assessment and Dose-Response Characterization for the Carcinogenicity of Formaldehyde by the Route of Inhalation. Health Canada and U.S. EPA. Ottawa. March 1998.
31. Co-chair. Workshop to explore the feasibility of an international collaborative study on use of cellular phones and risk of cancer. International Agency for Research on Cancer. Lyon. Feb 1999.
32. Panellist. Consensus Meeting for a Proposed Integrated National Health Surveillance Network. Health Canada. 1999.
33. Invited participant. Medical Research Council Summit Meeting on the new Canadian Institutes of Health Research. Toronto. June, 1999.
34. Invited participant. Planning group for an Institute of Population Health Research in CIHR. Jul-Dec 1999.
35. Invited speaker. Workshop for a Canadian Institute for Genetics Research. May 2000.
36. Invited participant. Workshop to explore the use of prospective cohorts to investigate gene-environment interactions in cancer etiology. National Cancer Institute. Rockville, MD. May 2000.
37. Invited participant. Founding meeting of Canadian Association for Workplace Safety and Health. Montréal. Jan 2001.
38. Invited participant. Workshop to advise Canadian Foundation for Innovation on its role in supporting population health research in Canada. Toronto, Feb 2001.
39. Invited participant. Consultative committee to advise Cancer Care Ontario on priorities in environmental cancer. April 2001.
40. Invited participant. Workshop on national priorities in cancer research. Institute for Cancer Research. CIHR. Toronto. May 2001.
41. Invited participant. Delphi process to advise Canadian Institutes of Health Research on priorities in cancer research. October-December 2001.
42. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
43. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.
44. Member of Advisory Panel. U.S. National Cancer Inst. Study of a Cohort of Chinese Workers Exposed to Benzene. 2002- .
45. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
46. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.

47. Organizer and Session Chair. International Epidemiological Association Meeting. Occupation and Health. Montréal. August, 2002.
48. Co-Organizer and Session Chair. Epidemiological Association Meeting. Asbestos and mesothelioma. Montréal. August, 2002.
49. Session Chair. Epidemiological Association Meeting. Environment and Health. Montréal Aug, 2002.
50. Invited participant. CIHR National Forum to devise a National Research Programme for Environmental Health. Ottawa. Sept 2002.
51. Invited participant. CIHR national forum on privacy of health data. Ottawa, November, 2002.
52. Member. Environmental and Occupational Carcinogens Advisory Group. Canadian Cancer Society. 2002 - 2004.
53. Participant. Meeting to discuss the establishment of a prospective childhood cohort in Canada. CIHR-IPPH. March 2004.
54. Member of working group on national cohort project. National Cancer Research Initiative. January-June 2004.
55. Member of advisory group on development of IDEES, Université de Montréal. January-June 2004.
56. Member, ad-hoc group to explore the feasibility of a Canadian cohort on cancer and chronic disease. 2004-2008.
57. Invited participant. Workshop to discuss the enhancement of population health research in Canada. CIHR-IPPH. June 2004.
58. Invited participant. Workshop on occupational cancer surveillance. Occupational Cancer Research & Surveillance Project (Cancer Care Ontario and the Ontario Workplace Safety & Insurance Board). February 2005.
59. Invited participant. Workshop on long-term large-scale cohorts. CIHR, December 2005.
60. Member. Advisory Scientific Committee. IBM – University of Alabama project on health of IBM manufacturing plant workers. 2006 - 2008.
61. Advisor and meeting participant. Ontario Workplace Safety and Insurance Board. Recommendations on how to develop occupational cancer research in Ontario. Toronto, 2005.
62. Invited participant. Workshop to estimate the burden of occupational cancer in the United Kingdom. UK Health and Safety Executive. Manchester. June 2006.
63. Advisory Committee to British Energy Networks Association. Workshop on the Future Needs of Electromagnetic Fields Occupational Studies in the Electric Utility Industry. Edinburgh. September 2006.
64. Advisory Committee. IARC Monograph Programme Planning of Special Volume 100. Lyon. September 2006.
65. Grant Review Panel. IVRSP. Paris. September 2006.
66. Advisory Committee to CCRA and ICR (CIHR) on the nature of a national cohort platform. Toronto, September 2006.
67. Invited participant. Comité d'éthique de la recherche de la faculté de médecine (CERFM) : Discussion d'un projet soumis pour la création d'une banque de données et de matériaux biologiques (Research Ethics Committee of the Faculty of Medicine: Review of a submitted project to create a bank of data and biologic samples). Université de Montréal. March 2007.
68. Invited participant. Workshop to Design and Implement the Ontario Cohort Consortium Research Platform. Toronto. June 2007.
69. Invited participant. Canadian Cancer Research Agencies. Strategic Planning Consultation in Montréal. May 2009.
70. Invited participant. IARC-NORA workshop to identify gaps of knowledge on occupational carcinogens, Lyon. June 2009.
71. Consultant. State of the science workshop: evaluation of epidemiological data consistency for application in regulatory risk assessment. US EPA and Johns Hopkins School of Public Health. Baltimore. September 2010.
72. Consultant. World Health Organisation. Re-evaluation of Risk Assessments related to DDT exposure. Geneva. November 2010.

73. Invited participant. WHO workshop to develop international guidelines for control of environmental carcinogens. Asturias. March 2011.
74. Session Chair. Discovering occupational carcinogens. Congress of Epidemiology. Montréal June 2011.
75. Invited co-organiser. Symposium of Environment and Cancer. Canadian Cancer Research Conference. Toronto. November 2011.
76. Invited organiser and Chair. Symposium on Cellphones and Cancer. American Association for Cancer Research. Chicago, April 2012.
77. Member Scientific Program Committee for the 2013 Canadian Cancer Research Conference, Toronto. November 2013.
78. Member of Advisory Committee to National Cancer Institute (U.S.) study on carcinogenicity of diesel emissions. 2017.

HONOURS

1. Biographee in various Who's Who in America versions. Since 1982
2. Perron-Desrosiers Prize. Granted by the Governing Council of the Institut Armand-Frappier. 1985.
3. Invited to give the annual Elizabeth Stern Memorial Lecture in U.C.L.A. School of Public Health. 1985.
4. National Health Scholar. National Health Research and Development Programme of Canada. 1988-1998.
5. Visiting Scientist Award. International Agency for Research on Cancer, Lyon. 1996-97.
6. Prix d'excellence. Institut national de la recherche scientifique. Université du Québec. 1999.
7. Distinguished Scientist Award. Medical Research Council, Canada. 1999-2004.
8. Canada Research Chair in Environmental Epidemiology and Population Health. 2001-2015.
9. Distinguished Scientist Lecturer. US National Cancer Institute. Division of Cancer Epidemiology and Genetics. 2006.
10. Cancer Research Society-Guzzo Chair in Environment and Cancer. Since 2007.
11. Fellow Canadian Academy of Health Sciences. Since 2008.
12. Geoffrey R Howe Distinguished Contributions Award, Canadian Society for Epidemiology & Biostatistics. 2011.
13. Ranked top Canadian public health researcher in terms of research productivity by Jarvey et al. 2012.

GRANT REVIEW, JOURNAL REVIEW AND PERSONNEL REVIEW

Associate Editor

American Journal of Epidemiology (1989-1998)

International Journal of Environmental Health (1991-)

Contributing Editor

Journal of Public Health Policy (1982-87)

American Journal of Industrial Medicine (1996-)

The Open Epidemiology Journal (2007-)

Chairman of grant review panels

National Health Research and Development Programme. Canada. (1990-94)

National Cancer Institute of Canada (1994-1995)

Member of grant review panels

40 times

External referee for tenure or promotion of personnel in other institutions

15 times

THESES

1. Siemiatycki J. "Space-time clustering: finding the distribution of a correlation-type statistic". M.Sc. thesis, McGill University, 1971.
2. Siemiatycki J. "Evaluation of strategies for household health surveys". Ph.D. thesis, McGill University, 1976.

ARTICLES PUBLISHED PEER REVIEW

1. Thurlbeck WM, Horowitz I, Siemiatycki J, Dunnill MS, Maisel JC, Pratt P, et al. Intra- and inter-observer variations in the assessment of emphysema. *Archives of Environmental Health*. 1969;18:646-59.
2. Becklake MR, Fournier-Massey G, McDonald JC, Siemiatycki J, Rossiter CE. Lung function in relation to chest radiographic changes in Quebec asbestos workers. *Bulletin de Physio-Pathologie Respiratoire*. 1970;6:637-59.
3. McDonald JC, McDonald AD, Gibbs GW, Siemiatycki J, Rossiter CE. Mortality in the chrysotile asbestos mines and mills of Quebec. *Archives of Environmental Health*. 1971;22:677-86.
4. Siemiatycki J, McDonald AD. Neural tube defects in Quebec: a search for evidence of 'clustering' in time and place. *British Journal of Preventive and Social Medicine*. 1972;26:10-4.
5. Siemiatycki J. Mantel's space-time clustering statistic: computing higher moments and a comparison of various data transforms. *Journal of Statistical Computation & Simulation*. 1978;7:13-31.
6. Siemiatycki J. A comparison of mail, telephone, and home interview strategies for household health surveys. *American Journal of Public Health*. 1979;69(3):238-45.
7. Siemiatycki J, Brubaker G, Geser A. Space-time clustering of Burkitt's lymphoma in east Africa: analysis of recent data and a new look at old data. *International Journal of Cancer*. 1980;25:197-203.
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* First author was under supervision of J. Siemiatycki when this work was carried out.

BOOK CHAPTERS (invited) AND IARC MONOGRAPHS

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76. Siemiatycki J. Risques de cancers reliés aux expositions chimiques en milieu de travail: résultats d'une étude épidémiologique à Montréal. IRSST, Montréal, November 1992.
77. Siemiatycki J. Carcinogens in the occupational environment. Invited seminar in School of Public Health, University of North Carolina, Chapel Hill, North Carolina. December 1992.
78. Siemiatycki J. Discussant of invited seminar on risk assessment. School of Occupation Health, McGill University, March 1993.
79. Siemiatycki J. Are the effects of smoking on lung and bladder cancer confounded by occupational carcinogens? Invited seminar given at the Michigan Cancer Foundation, Detroit and at the University of Michigan, Ann Arbor, May 1993.
80. Siemiatycki J. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? McGill University, Department of Epidemiology and Biostatistics, Montréal, December, 1993.
81. Siemiatycki J. Occupational causes of cancer. President's Cancer Panel Meeting on Avoidable Causes of Cancer, Bethesda, April 1994.
82. Siemiatycki J. Retrospective exposure assessment in community-based studies. Conference on Retrospective assessment of occupational exposures in epidemiology, IARC, Lyon, April 1994.
83. Siemiatycki J. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? Department of Human Oncology, University of Torino, Torino, Italy, April 1994.
84. Siemiatycki J. Risque de cancer dû au tabagisme. Département de médecine sociale et préventive, Université Laval, Québec, May 1994.
85. Siemiatycki J. Registry studies of bladder cancer. NCI Workshop on Occupational Exposures and Urogenital Cancers, Rockville, May 1994.
86. Siemiatycki J. Facteurs de risques environnementaux pour le cancer: une perspective épidémiologique. Atelier sur la recherche en cancer, Université du Québec à Rimouski, April 1995.
87. Camus M, Siemiatycki J. Non-occupational exposure to asbestos: how to assess dose and risk. McGill University, Department of Epidemiology and Biostatistics. Montréal, May 1995.
88. Siemiatycki J. Occupational carcinogens in Montréal. Seminar - International Agency for Research on Cancer, Lyon, France, June 1995.
89. Siemiatycki J. Occupational causes of cancer: findings from a large scale case-control study of occupational cancer. Department of Medical Informatics, Biometry and Epidemiology, University of Essen, Essen, Germany, July 1995.
90. Siemiatycki J. Assessing occupational exposures in community based epidemiological studies. Bremen Institute for Preventive and Social Medicine, Bremen, Germany, July 1995.
91. Case, B, Camus M, Richardson L, Siemiatycki J. Ascertainment of mesothelioma among Québec women from 1970 to 1990. Special Symposium on Mesothelioma, IRSST, Montréal, August 1995.
92. Siemiatycki, J. Une nouvelle approche épidémiologique pour le dépistage de cancérrogènes en milieu de travail. Club de recherches cliniques du Québec, Bromont, Quebec, September 1995.
93. Siemiatycki J. Occupational causes of cancer: findings from a large scale case-control study of occupational cancer. Special seminar. School of Public Health, Univ. of Michigan, Ann Arbor, Michigan, June 1996.
94. Siemiatycki J. An empirical evaluation of the magnitude of confounding bias. Statistical Society of Canada, Waterloo, June 1996.

95. Siemiatycki J. Occupational exposures and cancer risk: recent results and methodological insights from a population-based case-control study in Montréal. Department of Epidemiology & Biostatistics, McGill University. October, 1996.
96. Siemiatycki J. Utilités et limites des études épidémiologiques dans l'évaluation des risques environnementaux. ACFAS, City of Québec, Quebec, May 1998.
97. Siemiatycki J. International collaboration in cancer epidemiology. Society for Epidemiology Research, Chicago, June 1998.
98. Siemiatycki J. Accuracy of the EPA risk assessment model for predicting the risk of lung cancer at environmental levels of asbestos exposure. National Cancer Institute, Rockville, Maryland, March 1999.
99. Siemiatycki J. Risk of lung cancer at environmental levels of asbestos exposure. University of Toronto, Toronto, September 1999.
100. Siemiatycki J. Estimating risks due to low level exposures. Society for Epidemiology Research, Seattle, June 2000.
101. Siemiatycki J. Debater on the proposition that research is a top priority in occupational cancer prevention. Preventive Oncology Seminar, Cancer Care Ontario, Toronto, April 2001.
102. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondre K. Various aspects of smoking behavior on lung cancer risk: a flexible modeling approach. National Cancer Institute, Bethesda, May 2001.
103. Siemiatycki J. Challenges to epidemiology and challenges to Canadian epidemiologists. National Student Conference of Epidemiology, Toronto, June, 2001.
104. Siemiatycki J. President's address. Congress of Epidemiology, Toronto, June, 2001.
105. Siemiatycki J. Découvrir les cancérigènes dans l'environnement: bilan des activités de recherche passées et perspectives d'avenir. Département de médecine sociale et préventive, Université de Montréal, October 2001.
106. Siemiatycki J. Risque de cancer chez les femmes résidentes des villes des mines d'amianté québécoises: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque (« risk assessment ») du E.P.A. Département de santé environnementale, Université de Montréal, October 2001.
107. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Relations dose-réponse entre la fumée de cigarette et le cancer pulmonaire à partir d'une étude cas-témoins à Montréal : Estimations utilisant une modélisation flexible. Congrès INRS-Institut Armand-Frappier, Sainte-Adèle, Quebec, November 2001.
108. Siemiatycki J, Camus M, Case B, Desy M, Parent, M.-É. Risque de cancer chez les résidentes des villes de l'amianté au Québec: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque de l'E.P.A. Symposium sur l'amianté of Institut national de santé publique du Québec, Montréal, December 2001.
109. Laplante O, Parent M.-É, Siemiatycki J. Risque de mésothéliome et de cancer du poumon associé à l'exposition professionnelle aux fibres d'amianté, Montréal 1979-85. Symposium de l'Institut national de santé publique du Québec, Montréal, December 2001.
110. Siemiatycki J. Occupational causes of cancer: overview of the contribution of a study in Montréal, Research Day at Dept of Epidemiology and Community Medicine, University of Ottawa, April 2002.
111. Siemiatycki J. Biostatistical problems in epidemiologic case-control studies. Statistical Society of Canada, Hamilton, Ontario, May 2002.
112. Leffondre K, Abrahamowicz M, Siemiatycki J. Definition of risk sets for Cox's analysis of case-control data with time-varying exposures: A simulation study. Intended Society for Clinical Biostatistics (ISCB), Dijon, France, September 2002.
113. Siemiatycki J. Occupational causes of cancer. CCERN and Health Canada Research Workshop, Montebello, Quebec. October 2002.
114. Siemiatycki J. Occupational causes of cancer. Departmental seminar, McGill University, Montréal. November 2002.
115. Siemiatycki J. Facteurs environnementaux dans l'étiologie du cancer. Retraite annuelle du centre de recherche du CHUM, St-Sauveur, Quebec. November 2002.
116. Siemiatycki J. Environmental and occupational causes of cancer. Seminar. Cancer Care Ontario, Toronto, February 2003.

117. Siemiatycki J. The state of epidemiology in Canada. Plenary address. CSEB Student Congress, Halifax, Nova Scotia, June 2003.
118. Siemiatycki J. Occupational cancer epidemiology: the evolving big picture. Distinguished Scientist Lecture, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville MD, October 2003.
119. Siemiatycki J. Challenges in cancer epidemiology. Meeting of the Institute Advisory Board of Institute for Cancer Research, CIHR, Montréal, June 2004.
120. Siemiatycki J. Keynote address. Occupation and cancer. International Association of Cancer Registries, Beijing, September 2004.
121. Siemiatycki J. Which cancers are most important, what are the associated occupational situations and which confounders are involved? Burden of Cancer Epidemiologic Workshops, Health and Safety Executive. Manchester, UK, November 2004.
122. Siemiatycki J. Occupational causes of cancer. New Strategies for Recognizing and Preventing Occupational Disease, Canadian Center for Occupational Health and Safety, Toronto, March 2005.
123. Siemiatycki J. Occupational causes of cancer. The Respiratory Epidemiology & Clinical Research Unit, Montréal Chest Institute, Montréal, March 2005.
124. Siemiatycki J. Environnement et cancer : quels sont les risques? Les Belles Soirées public lecture series, Université de Montréal, Montréal, April 2005.
125. Siemiatycki J. An overview of environmental, occupational & lifestyle causes of lung cancer. Cancer Axis, McGill University Hospital Centre Research Institute, Montréal, June 2005.
126. Siemiatycki J. Les règles des comités d'éthique vont amputer notre capacité de prévenir des maladies et sauver des vies. Réunion de FRSQ sur les banques de données et des matières biologiques, Montréal, June 2005.
127. Siemiatycki J. Introductory comments. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
128. Siemiatycki J. The burden of occupational cancer on workers and on society. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
129. Siemiatycki J. Revue des expositions professionnelles associées au cancer (Review of occupational exposures associated with cancer): pre-conference training session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
130. Siemiatycki J. Opening session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
131. Siemiatycki J. Impact de l'environnement et du milieu de travail sur le cancer : connaissances récentes. 9es Journées annuelles de santé publique (JASP), City of Québec, Quebec, November 2005.
132. Siemiatycki J. La recherche épidémiologique sur le cancer. Canadian Cancer Society - 2005 Annual Conference, City of Québec, Quebec, November 2005.
133. Siemiatycki J. Occupational EMF exposure and risk of cancer – methodological considerations. Workshop on the Future Needs of Electro-magnetic Fields Occupational Studies in the Electric Utility Industry, Edinburgh, September 2006.
134. Siemiatycki J. What is known about the modifiable causes of cancer and why we will not learn much more: Reflections on the decline of epidemiology as a tool to elucidate disease etiology. Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montréal, October 2006.
135. Siemiatycki J. Keynote Speaker. Environmental causes of cancer. 28th Annual Meeting of the International Association of Cancer Registries, Goiania, Brazil, November 2006.
136. Parent M.-E, Rousseau M.-C, Siemiatycki J, Boffetta P, Cohen A. Using the workplace as a window to study the role of diesel and gasoline engine emissions in lung cancer development. Invited abstract submitted to the Eleventh International Congress of Toxicology, Montréal, Quebec, July 2007.
137. Siemiatycki J. Keynote Speaker. The future of occupational epidemiology? 19th International Conference on Epidemiology in Occupational Health (EPICOH 2007), Banff, October 2007. *Occup. Environ. Med.* 2007 Dec; 64:46.

138. Siemiatycki J. Relationship between environmental risks and health of seniors. Workshop on Seniors' Health and the environment. Health Canada, Ottawa, February 2008.
139. Siemiatycki J. Freedom of research - is it threatening or threatened? Conference of Institutional Review Boards of Quebec, (4e Journées d'étude des CER), City of Québec, Quebec, October 2008.
140. Siemiatycki J. Cancer and Environment – Annual University of Montréal Medical Faculty Assembly, Montréal, December 2008.
141. Siemiatycki J. Impact de l'environnement et du milieu de travail sur les risques de cancer : méthodologie de recherche et résultats. Conférence en santé publique, Université Laval, May 2009.
142. Siemiatycki J. CIHR and Epidemiologic Research. CSEB, Ottawa, May 2009.
143. Siemiatycki J. Mode de vie, milieu de vie: les causes modifiables du cancer. (Lifestyles and environment: modifiable causes of cancer). Keynote address. Conference nationale pour vaincre le cancer, Montréal April 2010.
144. Siemiatycki J. Montréal case-control studies on occupation and cancer. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
145. Siemiatycki J. Modifiable causes of cancer and estimates of attributable fractions. Presentation for II International Course on occupational cancer, Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
146. Siemiatycki J. Asbestos and cancer in Quebec: a presentation of studies in three populations. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
147. Siemiatycki J. An overview of recognized environmental and lifestyle causes of cancer, and their contribution to the overall burden of cancer. International Congress of Pathophysiology, Montréal, September 2010.
148. Siemiatycki J. Les causes modifiables du cancer (Lifestyles and environment: modifiable causes of cancer). Conference annuelle de la Société du cancer du Canada, division Québec, November 2010.
149. Siemiatycki J. Alison McDonald's research on the impact of Medicare in Québec. Department of Epidemiology and Biostatistics, McGill University, Montréal, Quebec, May 2011.
150. Siemiatycki J. An overview of environmental causes of cancer. Special Symposium to honour Nobel Prize winner CRCHUM, Montréal, Quebec, June 2011.
151. Siemiatycki J. Review of IARC evaluation on cellphones and cancer. Congress of Epidemiology, Montréal, Quebec, June 2011.
152. Siemiatycki J. L'évidence concernant les risques de cancer liés à l'utilisation du téléphone cellulaire. Institut national de santé publique du Québec, October 2011.
153. Siemiatycki J. Do cellphones cause brain cancer? Canadian Cancer Research Conference, Toronto, November 2011.
154. Siemiatycki J. Do cellphones cause brain cancer? Canadian Center for Architecture. Public science lecture series, Montréal, Quebec, January 2012.
155. Siemiatycki J. Do cellphones cause brain cancer? McGill University Department of Epidemiology lecture series, Montréal, Quebec, March 2012.
156. Siemiatycki J. L'environnement et le risque de cancer. Table ronde. Conference annuelle de la Coalition Cancer, Montréal, Quebec, March 2012.
157. Siemiatycki J. An Overview of Modifiable Risk Factors for Cancer. CHUM Department of Medicine, Montréal, Quebec, March 2012.
158. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Grand Rounds, St-Mary's Hospital, Montréal, Quebec, September 2012.
159. Siemiatycki J. The epidemiology of cell phones and brain cancer. Centre hospitalier universitaire Vaudois, Lausanne, Suisse, October 2012
160. Siemiatycki J. Occupational causes of cancer. Annual meeting of Occupational & Environmental Medical Association of Canada, Montréal, Quebec, September 2013.
161. Siemiatycki J. Fraction of lung cancer that is legally attributable to smoking: a novel parameter. ISPED, Bordeaux, France, November 2013.

162. Siemiatycki J. Some challenges in environmental cancer research. Boston University School of Public Health, Boston, Massachusetts, February 2014.
163. Siemiatycki J. Les causes modifiables du cancer: le cancer peut être évité. Symposium de La Fondation Sauve Ta Peau, Montréal, Quebec, September 2014.
164. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. BIPS, Bremen, Germany, September 2015.
165. Siemiatycki J. Insights into the use of epidemiologic data in a class action lawsuit against the tobacco industry. CRCHUM division seminar, Montréal, Quebec, September 2015.
166. Siemiatycki J. Development of a methodology to estimate legally attributable fraction of lung cancer attributable to cigarette smoking. McGill Univ Dept of Epidemiology, Montréal, Quebec, October 2015.
167. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. SIRIC-BRIO Cancer Centre. Bordeaux, France, November 2015.
168. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Dept of Medicine, CHUM, Montréal, Québec, November 2015.
169. Siemiatycki J. Occupation and cancer. Conference for the 50th Anniversary of IARC, Lyon, June 2016.
170. Siemiatycki J. Contribution of epidemiology to knowledge on occupational risk factors for cancer. 34e Congrès national de Médecine et Santé au Travail, Paris, France, June 2016.
171. Siemiatycki J. The influence of JC McDonald on the evolution of epidemiology in Canada. Symposium in honour of JC McDonald. McGill Univ., Montréal, Quebec, May 2017.
172. Siemiatycki J. A survey of knowledge on occupational causes of cancer. Keynote address. International Association of Cancer Registries, Utrecht, Netherlands, October 2017.
173. Siemiatycki J. La preuve statistique au tribunal : recours collectif en situation d'incertitude. Café-statistique de la Société des statisticiens français de la région parisienne, Paris, France, May 2018.

SCIENTIFIC PRESENTATIONS - OFFERED AND ACCEPTED

1. Siemiatycki J. Comparison of mail, telephone and home interview methods for health surveys. International Epidemiologic Association Meeting. Puerto Rico. August 1977.
2. Siemiatycki J, Day NE, Fabry J, Cooper, JA. Identification d'agents cancérigènes dans le milieu de travail: un nouveau système épidémiologique de monitoring. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
3. Siemiatycki J, Richardson L, Pless B. Equality in Medical Care under National Health Insurance in Montréal. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
4. Siemiatycki J. Discovering occupational carcinogens. International Symposium on Chemical Mutagenesis, Human Population Monitoring and Genetic Risk Assessment. Ottawa. October 1980.
5. Siemiatycki J, Richardson L, Gerin M. Discovering occupational carcinogens by a substance-based case-control approach-fieldwork considerations. International Epidemiologic Association Meeting. Edinburgh. August 1981.
6. Siemiatycki J, Colle E, West R, Belmonte M. Space-time clustering of juvenile-onset diabetes in Montréal. International Epidemiologic Association Meeting. Edinburgh. August 1981.
7. Siemiatycki J, Gerin M, Richardson L. Discovering occupational carcinogens by an exposure-based case-control approach: exposure assessment aspects. Second International Symposium on Epidemiology in Occupational Health. Montréal, August 1982.
8. Siemiatycki J, Gerin M, Lakhani R, Dewar R, Pellerin J, Richardson L. Nickel and cancer associations from a multicancer occupation exposure case-referent study. Symposium on Nickel in the Environment. Lyon, March 1983.
9. Gerin M, Siemiatycki J. La traduction des histoires professionnelles en histoires d'expositions chimiques: un défi pour l'hygiéniste du travail. Congrès de l'Association pour l'hygiène industrielle du Québec. Quebec, May 1983.
10. Siemiatycki J, Colle E, Campbell S, Belmonte M. Preliminary analysis of a case-control study of Type I diabetes mellitus. Baltimore, June 1985.

11. Siemiatycki J, Richardson L, Gerin M, Goldberg M, Dewar R. Associations between nine sites of cancer and nine organic dusts: results from a hypothesis-generating case-control study in Montréal. Society for Epidemiologic Research. Chapel Hill, North Carolina, June 1985.
12. Richardson L, Siemiatycki J, Gerin M, Goldberg M, Dewar R, Desy M, Campbell S, Wacholder S. Associations between several sites of cancer and nine organic dusts: results from a case-control study. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
13. Richardson L, Siemiatycki J. Case-control study methods: when to interview subjects and non-response bias. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
14. Soskolne C, Jhangri G, Checkoway, Risch H, Siemiatycki J, et al. Sulphuric acid exposure in laryngeal cancer: induction and latency estimates from a lagged exposure window analysis. XII Scientific Meeting of the International Epidemiology Assoc. Los Angeles, August, 1990.
15. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1989). Gastrointestinal illness and drinking water: a prospective epidemiological study. 57th Conjoint Meeting on Infectious Diseases (CACMID), Montréal, 25-29 November 1989, Résumé C-30.
16. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). Drinking water related gastrointestinal illnesses. 1990 Annual Meeting of the American Society for Microbiology, Anaheim California, 13-17 May 1990.
17. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). A prospective epidemiological study of drinking water related gastrointestinal illnesses. International Association on water Pollution Research and Control, Health Related Water Microbiology Group, Tubingen, West Germany, 1-6 April 1990.
18. Case BA, Dufresne A, Siemiatycki J, Fraser R. Decoding occupational history from total lung particulate analysis. II: A comparative study. Brit. Occ. Hyg. Soc.; Seventh International Symposium on Inhaled Particles, Edinburgh, September 1991, S4.5.
19. Suarez-Almazor M, Soskolne C, Fung K, Jhangri G, Burch D, Howe G, Miller A, Siemiatycki J, Lakhani R, Dewar R. Choice of summary worklife exposure measures in the estimation of risk: an empirical assessment. Canadian Epidemiology Symposium. Edmonton. May. 1991.
20. Siemiatycki J, Nadon L, Dewar R. Cancer risks due to occupational exposure to polycyclic aromatic hydrocarbons. 8th International Symposium on Epidemiology in Occupational Health, Paris, France, September 1991.
21. Bourbonnais R, Siemiatycki J. Socioeconomic variables and cancer risk. Canadian Society for Epidemiology and Biostatistics. Edmonton, May 1991.
22. Gerin M, Begin D, Siemiatycki J, Dewar R. Study on the validity of the NOES job-exposure matrix using industrial hygiene measurements obtained in Montréal. Conference on Retrospective Assessment of Occupational Exposure. IARC Lyon. April 1994.
23. *Camus M, Siemiatycki J. Estimating past asbestos fiber levels in the general population of asbestos mining towns in Quebec. International Society Environmental Epidemiology, Research Triangle Park, N.C. Sept. 1994.
24. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. Canadian Society for Epidemiology and Biostatistics. St-John's, Newfoundland, Aug 1995.
25. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. International Society for Environmental Epidemiology. Noordwijkerhout, Netherlands, Aug, 1995.
26. Case BW, Camus M, Siemiatycki J. Trends in Pathologic Diagnosis of Malignant Mesothelioma among Quebec Women 1970-1990. Royal College of Medicine. Montréal. Sept. 1995.
27. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational Risk Factors for Prostate Cancer. Canadian Society for Epidemiology and Biostatistics, St-John's, Newfoundland, Aug 1995.
28. *Camus M, Siemiatycki J. The Estimation of Past Asbestos Fiber Levels in Quebec Asbestos Mining Towns from 1900 to 1984. Canadian Society for Epidemiology & Biostatistics, St-John's, Newfoundland, Aug 1995.

29. *Camus M, Siemiatycki J, Dewar R. Non-Occupational Asbestos Exposure and Risk of lung Cancer in the Female Population of Asbestos-Mining Towns: Implications for Risk Assessments. Canadian Society for Epidemiology and Biostatistics Meeting, St-John's, Newfoundland, Aug 1995.
30. Payment P, Franco E, Siemiatycki J, Richardson L, Renaud G, Prevost M. Epidemiology studies of tap-water related gastrointestinal illnesses. Water Quality Technology Conference, New Orleans, Nov. 1995.
31. *Fritschi L, Siemiatycki J. Self-assessed versus expert-assessed occupational exposures. Canadian Society for Epidemiology and Biostatistics Meeting, St Johns, Newfoundland, Aug 1995.
32. Payment P, Siemiatycki J, Richardson L, Renaud G. Épidémiologie des maladies gastro-intestinales et respiratoires: incidence, fraction attribuable à l'eau et coûts pour la société. ACFAS, Montréal, May 1996.
33. *Fritschi L, Parent M-É, Siemiatycki J. Gastric cancer and occupation. Australasian Epidemiological Association, Victoria, Australia. July 1996.
34. *Camus M, Case BW, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.1: Environmental exposure assessment. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
35. Case BW, Camus M, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.2: Mesothelioma: observed vs. predicted. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
36. *Camus M, Siemiatycki J. Cancer risks due to non-occupational asbestos exposure. Can. Soc. for Epidemiol. & Biostat. London, Ontario, May 1997.
37. Weston TL, Aronson KJ, Howe GR, Nadon L, Siemiatycki J. Cancer mortality risk in a cohort of working men. Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
38. *Parent M-É, Siemiatycki J, Menzies L, Fritschi L, Colle E. Can Bacille-Calmette Guérin vaccination prevent insulin-dependent diabetes mellitus (IDDM)? Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
39. Wolf, S, Siemiatycki J, Beyersmann, D, Jockel, K. H. A case-control study of lung cancer - performance of a job-exposure matrix for cadmium, chromium, nickel, and stainless steel dust. Internat. Epidemiol. Assoc. European Region Meeting. Munster, Germany, Sept. 1997.
40. *Parent, M.E. Siemiatycki J. Exposition professionnelle aux émissions d'essence et de diesel, et cancer du poumon. ACFAS, Quebec, May 1998.
41. *Parent M-É, Siemiatycki J, Boffetta P. Occupational exposure to gasoline and diesel engine emissions and lung cancer. Soc. Epid. Res, Chicago, June 1998.
42. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Occupational exposure to gasoline and diesel exhausts and lung cancer. Inter. Soc. Environ. Epid, Boston, August 1998.
43. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Gasoline and diesel engine emissions in the workplace and lung cancer. PREMUS-ISEOH '98, Helsinki, Finland, Sept. 1998.
44. Leffondre K, Abrahamowicz M, Rachet B, Siemiatycki J. Modeling smoking history: A comparison of different approaches. Congress of Epidemiology, Toronto, June 2001.
45. Fritschi L, Nadon L, Benke G, Lakhani R, Latreille B, Parent M-É, Siemiatycki J. Validation of expert assessment of occupational exposures X2001 – Occupational Exposure Assessment for Epidemiology and Practice, Gothenburg, Sweden, June 2001.
46. Parent M-É, Siemiatycki J, Desy M. Case-control study of occupational exposures and risk of prostate cancer among farmers. Case-control study of occupational exposures and risk of prostate cancer among farmers, Toronto, June 2001.
47. Siemiatycki J, Camus M, Parent M-É, Richardson L, Desy M, Case BW. Case-control study of pleural mesothelioma among women in Quebec chrysotile mining regions. Inhaled Particles IX (BOHS), Cambridge, United Kingdom, September 2001.
48. Jockel K-H, Wolf S, Ahrens W, Jahn I, Pohlabein H, Beyersmann D, Siemiatycki J. Cadmium as a human lung carcinogen. Jahrestagung der Deutschen Arbeitsgemeinschaft für Epidemiologie (DAE) [Annual convention of the German epidemiology working group], Garmisch-Partenkirchen, Germany, September 2001.

49. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Annual Meeting of the Statistical Society of Canada (SSC). Hamilton, Ontario. May 2002.
50. Parent M-É, Siemiatycki J, Desy M. Association between Alcohol Consumption and Each of 23 Types of Cancer in Men. Soc. Epid. Res, Palm Desert, California, June 2002.
51. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Society for Epidemiologic Research (SER), Palm Desert, California, June 2002.
52. Rachet B, Parent M-É, Siemiatycki J. Welding Fumes and Lung Cancer: A Case-Control Study, Soc. Epidemiol. Res, Palm Desert, California, June 2002.
53. Rachet B, Abrahamowicz M, Sasco A, Siemiatycki J. Flexible estimation of the distribution of lag in the effects of exposures and interventions. 34th Annual SER Meeting. Palm Desert, California. June 2002.
54. Abrahamowicz M, Mackenzie T, Leffondre K, Du Berger R, Siemiatycki J. Joint modeling of time-dependent and non-linear effects of continuous predictors in survival analysis, with application to reassess the impact of intensity of past smoking on the risks of lung cancer in ex-smokers. 17th International Workshop on Statistical Modeling, Chania, Greece, July 2002.
55. Parent M-É, Siemiatycki J, Desy M. Exposure to chemical agents during leisure activities and risk of non-Hodgkin's lymphoma. Inter. Epidemiology Association, Montréal, August 2002.
56. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. International Epidemiological Association (IEA), World Congress of Epidemiology, Montréal, Québec, August 2002.
57. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Exposure-response relationships between cigarette smoking and male lung cancer from a case-control study in Montréal: generalized additive model approach. International Epidemiology Association (IEA) XVI World Congress of Epidemiology. Montréal, Québec. August 2002.
58. Parent M-É, Rousseau M-C, Siemiatycki J, Desy M. Body mass index and male cancer incidence at twelve different sites. Body mass index and male cancer incidence at twelve different sites. Halifax, Nova Scotia, June 2003.
59. Desautels N, Siemiatycki J, Parent M.E. Association between lifetime consumption of coffee, tea, and soft drinks, and incidence of eleven types of cancer: a case-control study. CSEB 2003 Biennial Meeting. Halifax, Nova Scotia, June 2003.
60. Parent M-É, Siemiatycki J, Desy M. Association between beta-carotene intake and risk of cancer at several sites. Society for Epidemiologic Research, Atlanta, Georgia, June 2003.
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170. Grundy A, Ho V, Parent ME, Siemiatycki J, Koushik A. Lifetime recreational moderate-to vigorous physical activity and the risk of ovarian cancer by subtype. Poster presentation. 2016 American Institute for Cancer Research (AICR) Research Conference, North Bethesda, Maryland, 14-16 November 2016.
171. Grundy A, Ho V, Parent ME, Siemiatycki J, Koushik A. The impact of menopausal status on the association between moderate-to-vigorous physical activity among participants in the Prevention of OVarian Cancer in Quebec (PROVAQ) study. Oral Presentation. Canadian Society for Epidemiology and Biostatistics 2017 Biennial Conference, Banff, Alberta, 1 June 2017
172. Bowman JD, Vila J, Richardson L, Kincl L, Cardis E on behalf of the INTEROCC Study Group. Occupational Exposures to Radio-frequency Electric Fields Assessed for the INTEROCC Study of Brain Cancer. Oral presentation. American Industrial Hygiene Association conference, Seattle, Washington, 4-7 June 2017.
173. *Karumanchi S, Siemiatycki J, Hatzopoulou M. Some challenges in measuring ultra-fine particles and developing a land use regression model. Oral presentation. Canadian Society for Epidemiology and Biostatistics (CSEB) 2017 Biennial Conference, Banff, Alberta, 30 May 2017.
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175. Ho V, Xu M, Pintos J, Lavoué J, Abrahamowicz M, Rousseau M.C, Richardson L, Siemiatycki J. Occupational exposures to leaded and unleaded gasoline engine emissions and lung cancer risk. Canadian Cancer Research Conference, Vancouver, British Columbia, 5-7 November 2017.
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179. Zhu Y, Lavoué J, Parent MÉ, Siemiatycki J, Koushik A, Ho V. Occupational Physical Activity and Lung Cancer Risk among Participants of the Alberta's Tomorrow Project. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
180. *Karumanchi S, Siemiatycki J, Richardson L, Hatzopoulou M. Estimating exposure to Ultrafine Particles in the Greater Montreal Area among case-control study subjects: Comparison of classical land use regression model with a model based on Bayesian principles - Proposal. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
181. van Tongeren M, Dirkx E, Lavoué J, Siemiatycki J, Ho V. Assessment of Occupational Exposure to Endocrine Disrupting Agents. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.

* First author was under supervision of J. Siemiatycki when this work was carried out

GRANTS AND CONTRACTS RECEIVED

1. Comparison of three methods for conducting household health surveys; Nat. Health Res & Devel. Prog. (NHRDP); \$27,000; 1974-76.
2. Pilot study of a case-control monitoring system for discovering occupational carcinogens; Conseil de la recherche en santé (CRSQ); \$80,000; 1978-1980.
3. Établissement du jeune chercheur; CRSQ; \$15,000; 1979-80.
4. Analyse de santé auprès de 1600 ménages montréalais; Ministère des affaires sociales (MAS); \$12,708; 1980
5. Dépistage des facteurs cancérigènes de l'environnement professionnel montréalais: étude pilote; Commission des accidents du travail; \$59,093 ; 1980-82.
6. Registry of patients with Juvenile Onset Diabetes in Québec; NHRDP; \$35,478*; 1980-85; (P.I. Dr E. Colle).
7. Secondary analysis of a health survey in Montréal: methodologic issues and comparison of morbidity and health care utilization between social groups; NHRDP-H&W Can.; \$15,000; 1981-82.
8. Exposure-based case-control approach to discovering occupational carcinogens; NHRDP-H&W Can.; \$129,258; 1981-83.
9. An exposure-based case-control approach to discovering occupational carcinogens; NCIC; \$131,842; 1981-83.
10. Variation in sex ratios of cancer between geographic areas; NCIC; \$3,227; 1982-84.
11. Équipe associée en épidémiologie des cancers professionnels (Team grant); Institut de la recherche en santé et sécurité du travail (IRSST); \$1 120,000; 1982-85.
12. Formaldehyde et cancer; IRSST; \$9,500; 1983.
13. Retrospective cohort study in the Montréal fur industry; IRSST; \$34,019; 1983-85.
14. Statistical analysis of a case-control study designed to discover occupational carcinogens; NHRDP-H&W Can.; \$484,022; 1985-87.
15. Completion of chemical coding of exposures in a case-control study designed to discover occupational carcinogens; IRSST; \$102,180; 1986.
16. Risks of cancer due to exposure to asbestos in a range of occupations; IRDA; \$61,206; 1986-87.
17. Biological estimation of exposure: a tissue registry for the identification and quantification of occupational carcinogens; NCIC; \$3,500*; 1986-87; (P.I. Dr B. Case)
18. Development of a proposal to study cancer risk and non-occupational exposure to asbestos; H&W Can.; \$29,500; 1987-88.
19. Evaluation of cancer risk and occupational exposure to formaldehyde; H&W Can.; \$30,000; 1987-88.
20. A genetic-epidemiologic study of breast cancer; NIH-NCI; \$90,945(US)*; 1987-92; (P.I. Dr. R. Haile).

21. Scholar award; NHRDP-H&W Can.; \$298,689; 1987-93.
22. An intervention trial to assess the risks of gastro-intestinal illness associated with consumption of treated tap water; NHRDP; \$225,000*; 1987-89; (P.I. Dr P. Payment).
23. Evaluation of cancer risk and occupational exposure to polycyclic aromatic hydrocarbons; H&W Can.; \$29,500; 1988-89.
24. Evaluation of cancer risk and occupational exposure to benzene, toluene and xylene; H&W Can, \$40,000; 1988-89.
25. Health risks due to chrysotile asbestos in the non-occupational environment: a workshop to evaluate a research protocol; H&W Can, \$20,000; 1988-89.
26. A population-based, case-control study of occupational exposure to sulphuric acid and the development of laryngeal cancer: an augmented secondary data analysis; NHRDP; \$11,120*; 1988-89; (P.I. Dr. C. Soskolne).
27. Mortality due to asbestos in the general environment of the Quebec mining areas; H&W Can.; \$130,000; 1989-90.
28. A case-control approach to discovering occupational carcinogens: an analysis of data; NHRDP; \$55,508; 1989-90.
29. Continued analysis of a large case control study of many types of cancer: occupational and non-occupational risk factors; NHRDP; \$463,827 1988-1992
30. Risk of cancer due to cigarette smoking - results of a multi-site case-control study; H&W Can.; \$30,000; 1989-90.
31. Étude sur la validité de matrice emploi-expositions multisectorielles; IRSST; \$18,207*; 1990-1992; (P.I. Dr. M. Gérin).
32. Équipe en épidémiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; \$526,297; 1990-1994.
33. Leukemia in children due to parental occupational exposures; NHRDP; \$108,000*; 1990-1994; (P.I. Dr Claire Infante-Rivard).
34. Risk of cancer due to exposure to chlorinated solvents - results of a multi-site case-control study; H & W Can.; \$30,000; 1991-92.
35. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer retrospective assessment of exposure; H & W Can.; \$60,000; 1991-92.
36. Feasibility of epidemiologic methods to investigate health outcomes near waste sites; H & W Canada; \$33,000; 1991-92
37. A pilot study to evaluate the prevalence of hip arthritis in the Montréal urban setting, and an evaluation of methods of recruitment of a population aged 65+; Montréal General Hospital Clinical Epidemiology; \$15,000*; 1991-92; (P.I. Dr. J. Esdaile).
38. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer; mesothelioma ascertainment; NHRDP; \$164,000; 1991-95.
39. Multivariate Regression Analyses of Occupational Risk Factors for Several Types of Cancers; NHRDP; \$128,827; 1992-96.
40. Development of a Job-Exposure Matrix for Use in Epidemiologic Case-Control Studies of Occupational Risk Factors; NHRDP; \$85,003; 1992-95.
41. A prospective epidemiological study of gastrointestinal health effects due to consumption of drinking water. E.P.A. (US)/ NHRDP/ Nat. Water Res. Inst.; \$300,000*; 1993-95. (P.I.: Dr. P. Payment)
42. A population-based, case-control study of occupational exposure to acidifying agents and the development of lung cancer: an augmented, secondary data analysis. NHRDP; \$72,220*; 1993-1995. (P.I. Dr. C. Soskolne).
43. Scholar award; NHRDP-Health Canada; \$126,990; 1993-95.
44. Équipe en épidémiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; \$242,652; 1994-1998.
45. Examen pathologique de cas présumés de mésothéliome recensés chez des femmes depuis 1970 dans des hôpitaux du québec. Health and Welfare Canada. \$30,000. 1994.

46. Cohort Study of a Ten Percent Sample of the Canadian Labour Force. NHRDP; \$12,000*; 1994-97. (P.I. Dr. K. Aronson)
47. A health survey of persons living near the Miron Quarry Sanitary Landfill site, Montréal: a pilot study. NHRDP; \$88,931 ; 1994-95. (P.I. Dr. M. Goldberg)
48. Occurrence of pathogenic microorganisms in water from St Laurent hydrological basin. FRSQ/ NHRDP & St Laurent Vision 2000; 1995-97. (P.I. P Payment)
49. Case-control study of lung cancer and environmental tobacco smoke; Health Canada; \$544,344; 1995-1997.
50. Case-control study of lung cancer and occupational exposures: NHRDP; \$840,000.; 1995-1998.
51. Occupational exposure to solvents and risk of breast cancer; National Cancer Institute of Canada; \$300,000*; 1995-1997. (P.I.: M Goldberg).
52. Scholar Award; NHRDP-Health Canada; \$263,329, 1995-1998.
53. Reanalysis of US data relating general mortality to air pollution; Health Effects Institute; 1998-2000 (P.I. D Krewski)
54. A case-control study of occupational risk factors for lung cancer; Medical Research Council of Canada; \$554,757, 1998-2001
55. Évaluation du risque de cancer du poumon et de mésothéliome associé à l'exposition à l'amiante chez les travailleurs de la région montréalaise; Ministère de la Santé et des Services sociaux; \$12,000. 1998.
56. Feasibility of a case-control study of the association between cell phone use and brain, salivary gland cancer and acoustic neurinoma. International Agency for Research on Cancer; \$12,000, 1998.
57. Inorganic particulate retained dose markers in lung cancer and mesothelioma. CIHR (P.I. Bruce Case) \$66,096. 1999-2003
58. Distinguished Scientist Award, Medical Research Council of Canada; \$330,000; 1999-2004.
59. Évaluation du risque de mésothéliome associé à l'exposition à l'amiante chez les femmes de la région minière; Ministère de la Santé et des Services sociaux; \$27,500. 1999-2000.
60. Program of research in environmental epidemiology of cancer (a national program to enhance capacity to conduct research) PREECAN; National Cancer Inst of Canada; \$1,000,000; 2000-2004.
61. Designing a national research agenda in environmental epidemiology of cancer. Medical Research Council of Canada Opportunities Program; \$40,000; 2000-2001.
62. Multi-centric case-control study of cell phone use and cancer risk in Montréal. CIHR; \$500,000; 2000-2004.
63. Trainee award for: Bernard Rachet, Post-doctoral fellow. PREECAN – NCIC; \$46,750; 2001-2003.
64. Cardiogene: a consortium to explore the gene-environment paradigm of major cardiovascular disorders in human and animal models. Canadian Institutes of Health Research, (P.I. P. Hamet) \$2,632,272; 2001-2007.
65. Canada Research Chair in Environmental Epidemiology. Federal CRC program. \$1,400,000; 2001-2008.
66. Installation of CRC. Canadian Foundation for Innovation. \$312,000; 2002-2004.
67. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 1). Canadian Cancer Society, Prostate Cancer Research Initiative, National Cancer Institute of Canada, (P.I. M-É Parent) \$947,360; 2002-2007.
68. Center for research on environmental etiology of cancer. For the application process. Centre Hospitalier de l'Université de Montréal (CHUM); \$7,000; 2002-2003.
69. Traffic-related air pollution and socioeconomic gradients in the incidence of cancer. CIHR, (P.I. M Goldberg) \$497,000; 2004-2007.
70. Development and validation of new statistical methods for modeling intermediate events in survival analysis. CIHR, (P.I. M Abrahamowicz) \$68,250; 2004-2005.
71. New survival analytic methods for time-dependent exposures in case-control studies, with applications to cancer. CIHR (P.I. K Leffondré) \$52,791; 2004-2007.
72. Trainee award for: Venkata Ramana Kumar, Post-doctoral fellow. PREECAN – NCIC; \$66,000; 2004-2007.

73. Environmental Cancer Research Team. Development grant for the preparation of the full team grant application. CIHR (P.I. J. Siemiatycki) \$9,500; 2005-2006.
74. Trainee award for: Franco Momoli, PhD student. PREECAN – NCIC; \$25,600; 2005-2006.
75. Occupational and selected non-occupational risk factors for lung cancer: Analysis of a case-control study in Montréal. CIHR (co-P.I.'s: J Siemiatycki & M-É Parent) \$1,920,447; 1999-2011.
76. Development and evaluation of a cost-effective approach for retrospective assessment of occupational exposures in population-based studies (pilot study). Canadian Cancer Etiology Research Network - NCIC (P.I. M-É Parent) \$35,000; 2006-2007.
77. Trainee award for: Aihua Liu, PhD student. PREECAN – NCIC; \$12,600; 2006-2007.
78. Prostate cancer and occupational whole body vibration. Ontario Workplace Insurance Board: Research Advisory Council; Solutions for Workplace Change (P.I. J Purdham); \$140,480; 2006-2008.
79. Guzzo-SRC Chair in Environment and Cancer. Cancer Research Society, \$1,285,000; 2007-2020.
80. INTEROCC: Occupational exposures and brain cancer. NIH (P.I. E Cardis: To support the analysis of the occupational component of an international case-control study involving 13 countries and coordinated at the International Agency for Research on Cancer of the WHO [France]); \$1,626,757 US; 2008-2010.
81. Development and validation of a lung cancer risk prediction model. NCIC (P.I. I Karp); \$102,099; 2008-2010.
82. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 2). NCIC (P.I.: M-É Parent); \$756,000; 2008-2011.
83. Preparation and development of an epidemiological study of modifiable and genetic factors associated with ovarian cancer risk (pilot project). Ovarian Cancer Canada (P.I.: A Koushik); \$28,330; 2008-2009.
84. SYNERGY - Pooled analysis of case-control studies on the joint effects of occupational carcinogens in the development of lung cancer: Montréal component. German Statutory Accident Insurance (DGUV) (P.I.: A Koushik); \$119,177; 2008-2010.
85. The risk of lung cancer related to occupational and recreation physical activity and to dietary intake of flavonoids. Canadian Cancer Research Society. (P.I.: A Koushik); \$208,317; 2009-2012.
86. A case-control study of modifiable and genetic factors associated with the risk of ovarian cancer. Canadian Cancer Society Research Institute (P.I: A Koushik); \$498,997; 2010- 2013.
87. Occupational and selected nonoccupational risk factors for lung cancer: analysis of a case-control study in Montréal. CIHR (P.I: J Siemiatycki, M-É Parent); \$850,620; 2011-2015.
88. Quebec Research Program for Prostate Cancer Prevention. Cancer Research Society (P.I.: M-É. Parent, P Karakiewics) \$4,728,203; 2011-2015.
89. Extreme weather and maternal-child health: targeting future impacts of climate change. CIHR. (P.I.: N Auger) \$85,333; 2015-2019.
90. Development of an instrument for assessing occupational exposures in cancer case-control studies and its application to cancers of lung, brain, ovary. Cancer Research Society- Programme GRePEC (Groupe de recherche et de prévention en environnement-cancer). (P.I.: J Siemiatycki, M Pollak) \$2,510,890; 2011-2018.
91. Occupational physical activity and lung cancer. (P.I.: V Ho, A Koushik).CIHR. \$75,000. 2017-2018.
92. Analyses of existing Canadian cohorts and databases related to occupational physical activity and lung cancer risk. CIHR. (P.I.: V Ho, A Koushik) \$74,989; 2017-2018.
93. The role of lifestyle factors in ovarian cancer prognosis. Department of Defence – Ovarian Cancer Research Program. (P.I.: A Koushik) \$216,458 USD (est. \$293, 000 CAD); 2015-2017. Extended August 2018.
94. Occupational Exposure to Endocrine Disrupting Chemicals and Colorectal Cancer risk. CIHR (P.I.: V Ho, J Siemiatycki) \$252,450; 2018-2021.
95. Occupational exposures of women: improvement of an existing job exposure matrix to provide gender-specific estimations of exposure. IRSST. (P.I.: V Ho) \$491,484; 2018-2021.

Exhibit 56

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
REBECCA SMITH-BINDMAN, MD**

Date: November 15, 2018



Rebecca Smith-Bindman, MD

The Relationship Between Exposure to Perineal Talc Powder Products and Ovarian Cancer

Expert Report

Rebecca Smith-Bindman, MD

Professor, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics,
Gynecology and Reproductive Science and Director, Radiology Outcomes Research Lab
University of California San Francisco

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I. Executive Summary

Substantial evidence supports a strong positive association between ovarian cancer and genital exposure to talcum powder products and that regular exposure to talcum powder products causes ovarian cancer in some women. Talc is a naturally occurring mineral used in cosmetic products because of its desirable chemical properties such as being soft and absorbent. Women who have had regular exposure of the genitals (specifically the perineal region from the pubic area to the anal area) to talcum powder products are at increased risk of developing invasive ovarian cancer, in particular serous cancer, the most common and most lethal form. In the United States, a substantial portion of women report having ever used talc powder products at some point in their life. The most commonly reported frequency of talcum powder product use is daily. Women who use talcum powder products daily increase their risk of developing ovarian cancer significantly. Regular exposure causes ovarian cancer in some women.

I was asked to review the medical and scientific literature regarding the relationship between genital talcum powder product use and ovarian cancer and determine whether the relationship is causal. For this extensive analysis and report, I applied the same methodology with the same scientific rigor that I use in my research and clinical practice. I reviewed 43 relevant publications presenting scientific data on the association between ovarian cancer and exposure to talc powder products: 4 cohort studies, 8 systematic reviews, 2 studies that pooled data from multiple individual studies, and 30 case-control studies. I also read numerous review articles, and systematic reviews on related topics such as those completed by the International Agency on Research on Cancer (IARC). I also completed my own, new systematic review on of the studies that I reviewed as part of this report. This report contains my overview of these publications plus a detailed new systematic review of the studies that I conducted. After reading, evaluating, and summarizing these publications, in my expert opinion, I do not have any uncertainty that regular exposure to talc powder products increases a woman's chance of developing epithelial ovarian cancer. In my expert opinion, regular exposure to talcum powder products causes ovarian cancer

Quantifying the precise magnitude of the association is more difficult than establishing the association. The association will certainly vary by demographic and reproductive factors and whether women have other underlying ovarian cancer risk factors and exposures. With that caveat, **it is my opinion that women exposed to perineal talc powder products on a regular basis have about a 50% increase in their subsequent risk of developing invasive serous ovarian cancer**, compared to women who do not regularly use talc and even after accounting for other ovarian cancer risk factors. This estimate is supported by existing publications and my quantitative review of the scientific literature that focused on summarizing studies that addressed regular exposure to talc powder products as a risk factor for epithelial ovarian cancer, and in particular serous cancer. Talcum powder exposure is associated with other epithelial cancer subtypes (in particular, clear cell and endometrioid carcinoma), but because these cancers are less common, and because fewer studies have evaluated these cancers in sufficient numbers, quantifying the associations is more difficult. While some publications estimated talc powder products have a slightly greater risk of these cancer subtypes, others

estimated a slightly lower risk of these cancer subtypes. In my opinion, this risk is likely overall in about the same range as for serous cancer, but I would estimate slightly less at 40% increased risk.

The epidemiological evidence documents a strong, positive association between exposure to talcum powder products and ovarian cancer and that regular exposure causes ovarian cancer. The epidemiological evidence alone does not confirm the mechanism by which talc powder product increases ovarian cancer risk, nor does it confirm the specific component in talcum powder products that makes it carcinogenic. Nonetheless, the literature provides compelling evidence that exposure to talcum powder products leads to chronic inflammation and that the inflammation induces a strong biological response that results in the induction, promotion, and growth of cancer. Further, there is evidence that several highly carcinogenic agents are components of the talcum powder products. These include, most importantly, asbestos, a Group 1 carcinogen that the International Agency for Research on Cancer (IARC) has determined causes ovarian cancer. I have seen evidence that talcum powder products contain asbestos. Second, talcum powder products contain asbestiform talc particles which have a similarity in structure to asbestos fibers (and which IARC concludes are carcinogenic). Lastly, talcum powder products contain numerous heavy metals such as, nickel, chromium, (Group 1 carcinogens) and cobalt (Group 2 carcinogen) according to IARC. These components are carcinogenic (cause cancer) and can contribute to the carcinogenicity of talcum powder products. Observational and experimental data confirm that talcum powder product particles applied to the perineum can reach the fallopian tubes and ovaries through the vagina, supporting that talc particles applied to the perineum can deposit on the ovaries. Surgery that impedes the movement of particles from the perineum to the ovaries such as hysterectomy (uterine removal) or tubal ligation (tying or blocking the fallopian tubes to the ovaries), reduces the elevated risk of ovarian cancer from exposure to talcum powder products. This finding supports that local tissue response and inflammation in the fallopian tubes and/or ovaries from talcum powder products (with components) causes the elevated ovarian cancer risk.

In summary, **from my review of the scientific literature and my own analysis, it is my opinion that genital exposure to talcum powder products is an actionable and causative risk factor for ovarian cancer.** As a physician involved in women's health issues, I view talcum powder usage as a modifiable "lifestyle" risk factor that should be avoided because of the substantial risk to health and lack of therapeutic benefit. An elevated risk of 50% is significant and results in a large number of unnecessary ovarian cancers given the large number of women exposed. Depending on estimates of how many women regularly use talcum powder products, between 7% and 20% of all ovarian cancers and 14% - 39% of invasive serous cancers (the most aggressive and feared cancer type) are caused by the use of talcum powder products. These cancers can be prevented if women do not use talcum powder products.

II. Qualifications

Education and Employment

I am a professor of Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Medicine, and Health Policy at the University of California San Francisco (UCSF) School of Medicine. I graduated from Princeton University with a degree in structural engineering (with combined majors in engineering and architecture) and attended UCSF medical school. My training after medical school included an internship, radiology residency, and clinical fellowship in women's health and a research fellowship in epidemiology and biostatistics in the UCSF Departments of Medicine and Epidemiology and Biostatistics.

I am a clinician-scientist. My clinical work includes one day a week in the Department of Radiology and Biomedical Imaging, with a focus on women's health imaging. I work in the ultrasound section, where a large proportion of the work is focused on the diagnosis of ovarian abnormalities (cancer and other functional issues). I run the UCSF Radiology Outcomes Research Lab, spending most of my time on clinical research and leading large epidemiological studies. I teach in the UCSF School of Medicine and Department of Epidemiology and Biostatistics.

Research Expertise

My research expertise is in epidemiology, outcomes research, comparative effectiveness, health services research, and dissemination and implementation sciences. My epidemiological studies have evaluated the quality, use, accuracy, predictive value, and impact of diagnostic testing on patient health. I have measured the risks and benefits of medical imaging in different contexts and different populations. Much of the research is in women's health, including diagnoses of cancers such as ovarian, endometrial, thyroid and breast. I have led many large, multi-institutional research projects. These projects are typically collaborative, involving researchers and clinicians with diverse expertise including radiology, obstetrics and gynecology, medicine, biostatistics, epidemiology, economics, demography, social sciences, medical informatics, radiation science, and dissemination and implementation science.

I have been a prolific researcher. I have led projects funded by more than 50 million dollars in research grants—entirely focused on cancer diagnosis and prediction. The research has been published in the most prestigious medical journals including the *New England Journal of Medicine*, *Annals of Internal Medicine*, *Journal of the American Medical Association*, *Journal of the American Medical Association Internal Medicine*, *Journal of the National Cancer Institute*, *Obstetrics and Gynecology*, and leading radiology specialty journals such as *Radiology* and *Journal of the American College of Radiology*.

Knowledge of Relevant Study Designs

Several of my published studies have been systematic, meta-analytic, quantitative reviews of the published literature. Meta-analyses review existing evidence on a topic and summarize

and re-analyze data from earlier studies. My systematic reviews focused on the diagnoses of endometrial cancer, breast cancer, and a range of birth defects including trisomy 21 (Down syndrome) and trisomy 18 (Edwards Syndrome). Many of my reviews were published in prestigious medical journals, reflecting their scientific rigor based on an in-depth understanding of how to combine and review results from different studies in a scientifically valid and reproducible way.

Several of my recent research projects quantified the variation in radiation dose associated with medical imaging and the expected impact of this variation on cancer outcomes. This work has brought attention to the need for better standards in medical imaging. I am currently leading two large, multi-institutional epidemiological projects on medical radiation funded by the National Institutes of Health. One project is collecting radiation dose measures associated with computed tomography (CT) imaging from more than 150 hospitals in the United States, Europe, and Asia and testing the impact of providing feedback and education to radiologists on average and high doses. The second project is a multinational epidemiological study on childhood cancer. This project is assessing the risk of cancer associated with medical imaging among 1 million children and 1 million pregnant patients after accounting for a range of other cancer risk factors. The study will be the first to quantify the risk of medical imaging including CT among a large group of patients and uses novel methods to accurately estimate radiation dose from imaging.

I have expertise in a range of research study designs. The projects I currently lead (each funded by the National Institutes of Health or the Patient-Centered Outcomes Research Institute for between 9 - 15 million dollars each) have designs selected to be appropriate for the research question. For example, the study assessing the risk of cancer from medical imaging uses a *case-control study design, in which data are collected on a group of patients and those with a condition (cases), are matched to similar patients without the condition (controls)*. Matching people with a disease to people of similar age, gender, and other factors who do not have the disease allows researchers to determine if circumstances such as exposure to a potential toxin influence disease development.

My project on medical imaging uses a *cohort design, comparing groups of people (cohorts) in a population, some exposed to a potential disease agent and some not exposed*, to see if the agent influences disease. My study on radiation doses from CT uses a *randomized controlled design, in which individual patients are randomly assigned to different treatments* so their effectiveness can be compared. I am studying lung nodules using a *cluster-randomized controlled trial design that randomly assigns groups of people in similar circumstances (for example because they all see the same doctor) to different treatments* so the effects of the treatments can be compared.

I have a deep understanding of how epidemiological studies are conducted. I understand what study designs are suitable to particular datasets, populations, and research questions and the advantages and disadvantages of each design. This is relevant as no single study

design is “best;” there are strengths and weaknesses of each. The most appropriate and valid study design varies based on the research question being asked.

Experience as a Medical Expert

For the National Academy of Medicine, I have contributed to several reports, including Saving Women’s Lives (2004), Improving Mammographic Quality Standards (2005), and Breast and the Environment: A Life Course Approach (2012), for which I wrote a review on the association between radiation exposure and breast cancer (Appendix). In addition to this research, I am actively involved in raising awareness of the need for better standards and greater safety around medical imaging, in particular related to radiation exposure. I have spoken at the US Food and Drug Administration, testified before the US Congress on several occasions, and worked with leading professional societies to focus attention on improving medical imaging safety. I have written several quality measures on radiation dose adopted by the National Quality Forum and developed educational tools to help physicians and patients understand the importance of minimizing radiation exposure from imaging.

Prior to providing my opinions on the association between talcum powder products and ovarian cancer, I had not reviewed the relevant literature and had not published in this area. As a result, I brought an unbiased perspective to my review. This report reflects my review of medical and scientific publications in this area (overviews and scientific studies), my own analysis, and review of documents shared with me by the lawyers who engaged me for this task. My curriculum vitae is attached as Exhibit A, the materials I considered are attached as Exhibit B, and my fees and prior testimony are attached as Exhibit C.

III. Background: Ovarian cancer and Talc as a Modifiable Risk Factor

Ovarian Cancer

Ovarian cancer is the seventh most common cancer in women and the fifth leading cause of cancer deaths in the United States. ¹ In 2018, 22,240 women are expected to receive a new diagnosis of ovarian cancer and 14,070 women will die from it. Overall, about 1 in 78 women (1.3%) will be diagnosed with ovarian cancer in their lifetime and around 1 in 108 will die of it. About 224,940 women are currently living with ovarian cancer. ² Most cases occur among older women; the median age at diagnosis is 62, although this varies by ovarian cancer type. ²Ovarian cancer is frequently diagnosed at a late stage, when a cure is unlikely. Because so many ovarian cancers are diagnosed at a late stage, the overall mortality rate is high, and the overall 5-year survival is poor. With the poor prognosis and absence of a reliable screening test to find ovarian cancer early, it is a highly feared cancer for women and their physicians alike.

Histologic types

Cancers are classified by histologic type, meaning the type of cells that are involved.

Understanding ovarian cancer histologic types is important because the risk factors, etiology and genetics of ovarian cancer can vary by histological type. Therefore, the importance of talcum powder products as a risk factor or cause can also vary by type.

Ovarian cancers (epithelial and non-epithelial) are a heterogeneous group of malignancies that vary in their pathological appearance, molecular biology, risk factors, etiology and prognosis.¹ Epithelial ovarian cancers have several histologic types; most fall into a small group of more common types including serous, endometrioid, clear cell and mucinous. About 90% of ovarian cancers are epithelial (meaning they arise from cells on the surface of the ovary or fallopian tube) and the most common type of epithelial cancer is serous carcinoma. Serous is not only the most common type of ovarian cancer, it is also the most lethal type of ovarian cancer. Further, it is the type of cancer that pathologists can most consistently, reliably, and reproducibly diagnose. Thus, epidemiological studies will have the greatest ability to document a clear association between serous ovarian cancer types and talcum powder products, if a connection exists. It is also the subtype that has been studied most from a molecular and pathologic research standpoint.

Table 1. Histologic Types of Ovarian Cancers Diagnosed Over 15 Years at the KP Washington (in press, JAMA Internal Medicine)

Histologic Type	Number	Percent of Total Cancers
Papillary serous cystadenocarcinoma	52	36.6
Endometrioid carcinoma	17	12.0
Serous cystadenocarcinoma	15	10.6
Clear cell adenocarcinoma	12	8.5
Adenocarcinoma, NOS	11	7.7
Mucinous adenocarcinoma	7	4.9
Mixed cell adenocarcinoma	3	2.1
Serous surface papillary carcinoma	3	2.1
Granulosa cell tumor	3	2.1
Carcinoma, not otherwise specific	2	1.4
Mucinous cystadenocarcinoma	2	1.4
Mucinous cystic tumor of borderline	2	1.4
Carcinoma in situ	1	0.7
Squamous cell carcinoma	1	0.7
Papillary adenocarcinoma	1	0.7
Papillary serous cystadenoma, borderline	1	0.7
Adenocarcinoma with squamous meta	1	0.7
Granulosa cell tumor, malignant	1	0.7
Endometrial stroma sarcoma	1	0.7
Mullerian mixed tumor	1	0.7
Carcinosarcoma	1	0.7
Carcinosarcoma, embryonal	1	0.7
Teratoma, malignant	1	0.7
Astrocytoma	1	0.7
Marginal zone B-cell lymphoma	1	0.7
Total	142	100
Summary		
Serous carcinoma	70	49.3
Endometrioid carcinoma	17	12.0
Clear cell carcinoma	12	8.5
Mucinous carcinoma	9	6.3

My research group recently reported on the ultrasound appearance of ovarian cancers among a large cohort of women. The purpose of this cohort study was to quantify the risk of malignant ovarian cancer based on ultrasound findings. We described 142 new ovarian cancer cases in a population of 500,000 women enrolled in Kaiser Permanente Washington, an integrated health plan, between 1997 and 2008, including 72,093 women who underwent pelvic ultrasound. The distribution of cancer histological types is in Table 1. Serous carcinoma was the most common cancer type: In our cohort, it was 50% of the ovarian cancers. Serous carcinoma has the worst prognosis of the ovarian cancer types. Its high frequency and poor

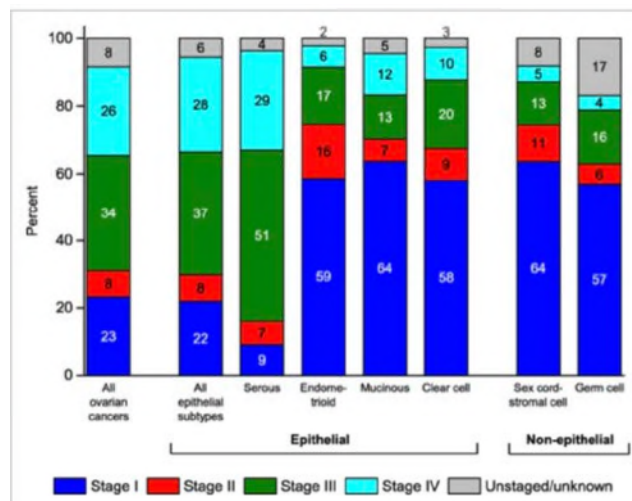
prognosis contribute to the high mortality rate for ovarian cancer overall. The other common histological types of ovarian cancer were endometrioid (12% in our data), clear cell (8.5% in our data), and mucinous (6.3% in our data).

Ovarian cancer types have large differences in stage of diagnosis (a strong predictor of survival) and prognosis independent of stage. The 5-year survival by histological type is in Table 2. Serous cancer is the most frequent and most aggressive, with an overall 5-year survival of 43% as compared with 82% for endometrioid. The survival is strongly influenced by stage at diagnosis, with higher stage numbers indicating more advanced stage.¹ Most serous carcinomas are diagnosed at stage III (51%) or IV (29%) (Figure 1),² for which 5-year survivals from the most recent data were 42% and 26%, respectively. These data reflect the aggressive nature of serous cancer.¹ In contrast, the majority (58% to 64%) of endometrioid, mucinous, and clear cell carcinomas are diagnosed at stage I, similar to nonepithelial tumors (Figure 1). Consequently, the 5-year survivals are 82%, 71%, and 66%, respectively, for endometrioid, mucinous, and clear cell carcinoma. Thus, these cancers behave very differently, even though all are ovarian epithelial cancers.

Table 2. Percent of Women Surviving 5 Years After Diagnosis by Epithelial Ovarian Cancer Type. Data From 2008–2013.

	All epithelial types	Serous	Endometrioid	Mucinous	Clear cell	Sex cord-stromal	Germ cell
Stage							
All	47	43	82	71	66	88	94
Stage I	89	86	95	92	85	98	99
Stage II	71	71	84	69	71	84	93
Stage III	41	42	59	30	35	61	90
Stage IV	20	26	29	13	16	41	69

Figure 1. American Joint Committee on Cancer Sixth Edition Stage Distribution (%) for Ovarian Cancer by Histology, US, 2007-2013, SEER 18 Registries, NCI, 2017. This shows that serious cancers are more likely to be diagnosed at state III, IV (green and teal), compared with other tumor types.



This summary reflects our current knowledge about ovarian cancer histologic types and their associated prognoses. As research results are reported, our knowledge will evolve. For example, recent studies suggest we need to improve our ability to distinguish between high-grade serous and endometrioid carcinomas. Other results suggest that many ovarian mucinous carcinomas are actually gastrointestinal tumors that metastasized to the ovaries and this realization is affecting the reported rates of ovarian mucinous carcinomas (which are declining).^{1,3,4} The categorization of noninvasive tumors classified as borderline is also under investigation and a topic of discussion in the field. These noninvasive tumors have historically been considered in the spectrum of ovarian cancer that have less aggressive behavior. However, many previously described borderline cancers are now generally considered non-malignant.

In summary, when assessing the carcinogenicity of talcum power products, this should focus on invasive serous carcinoma as the most important cancer (based on prognosis) and the most reliable cancer to identify (based on histology and understanding of cancer behavior).

Additionally, over the last decade, there has been research suggesting that many ovarian cancers originate from cells in the distal portion of the fallopian tube. Because the pathogenesis, treatment, and prognosis of serous cancers of the fallopian tube, ovary, and peritoneum are similar, these are now typically considered as a single entity.⁴ This consideration applies to the association with talcum powder product usage discussed in this report.

Risk Factors

Understanding ovarian cancer risk factors is important because analyzing the impact of talcum powder products exposure must consider *covariates, or other characteristics* that a woman might have that might also influence her ovarian cancer risk such as age, inherited genetic mutations, reproductive factors, or family history of cancer. Every risk factor does not have to be considered to come to a valid conclusion; indeed, this is not realistic within the limitations of medical research, and the bias introduced by the exclusion of some risk factors will be small. However, crude analyses that look at the risk of ovarian cancer from talcum powder products without adjusting for any other risk factors must be considered cautiously. For that reason, statistical analyses of research results often adjust for *confounding factors or variables that are covariates that hinder accurate calculation of an association*, for example between talcum powder products and ovarian cancer.

Numerous risk factors are identified for ovarian cancer.⁵ Unfortunately, few can be modified by therapies or lifestyle changes. Risk factors vary by histologic type⁵ but those that increase risk of ovarian cancer include personal or family history of ovarian or breast cancer, inherited mutations including BRCA1 and BRCA2⁶⁻¹⁰ advanced age, white race, increased education, and endometriosis. Other factors that may increase ovarian cancer risk due to estrogen exposure include having no pregnancies or advanced age at first birth, obesity, and postmenopausal hormone therapy.¹¹⁻¹³ Several factors are associated with reduced risk for ovarian cancer including breast feeding, multiple pregnancies, use of oral contraception,

tubal ligation, and removal of uterus, fallopian tubes, or both.¹⁴⁻¹⁸ Smoking is a possible risk factor for ovarian cancer, primarily mucinous subtype, although study results have not been consistent.^{5,19}

Risk factors vary by cancer type. For example, serous cancer is more strongly associated with reproductive risk factors than mucinous tumors²⁰⁻²² and different histologic types have different molecular and genetic profiles.²³⁻²⁵ Serous tumors are more likely to have a cancer-promoting mutation in the p53 gene, whereas similar KRAS mutations are more common in mucinous tumors. Over time, the occurrence of ovarian cancer has changed, in part due to changes in risk factors. For example, small declines in the rates of endometrioid and serous cancer are attributed to declining use of hormone replacement among postmenopausal women.

Etiology: Origins, Causes, Development and Inflammation

Our understanding of the etiology and course of ovarian cancer continues to evolve. Hereditary genetic predisposition increases risk, but overall, accounts for only a small proportion of cancers. And even in women with hereditary genetic mutations, not all will develop ovarian cancer. The majority of ovarian cancers are now believed to arise in the distal portion of the fallopian tube. By convention, fallopian tube, ovary and peritoneal cancers are considered as a single entity. The most widely accepted mechanism for initiation, promotion and progression of ovarian cancer is tissue inflammation leading to a series of responses that result in cancer.

There is very clear and extensive scientific literature describing the relationship between inflammation and cancer across many anatomic areas. Chronic inflammation, and even subtle, subclinical inflammation, is associated with an increased risk of cancer.²⁶⁻²⁸ Many inflammatory conditions predispose to cancer development. Diverse factors that lead to inflammation - infection, chemical exposures, physical agents, autoimmune factors, and even inflammatory reactions of uncertain etiology - can lead to an increase in cancer incidence. For example, there are well described and accepted causal pathways linking inflammation in the etiology of bladder cancer (schistosomiasis, toxic chemicals), cervical cancer (papillomavirus), gastric cancer (H Pylori), colon cancer (inflammatory bowel disease), liver cancer (hepatitis), mesothelioma (asbestos) and ovarian cancer (pelvic inflammatory disease and endometriosis). The biological pathways associated with inflammation include stimulation/interference with a range of biological responses that are involved in initiation of cancer, promotion of cancer, and progression of cancer. Oxidative stress resulting from inflammation can impact all stages of cancer development including cancer initiation (DNA is damaged by introducing gene mutations and structural alterations of DNA leading to inhibition of DNA repair and malignant transformation); promotion (which may be manifest as abnormal gene expression resulting in cell proliferation and decrease apoptosis) and progression (further DNA damage and enhancement of cell growth.²⁹ Local inflammatory response can lead to signaling molecules such as cytokines, chemokines, prostaglandins, growth transcription factors, microRNAs having higher expression that can promote cancer

development and can create a favorable microenvironment for the development and progression of cancer.³⁰ Inflammation impacts every step of tumorigenesis, from initiation through tumor promotion, and extending to metastatic progression. Similarly, the most compelling mechanism for the etiology of ovarian cancer is that of chronic inflammation and scarring in the ovary that leads to malignant transformation and cancer progression. This mechanism involves cell proliferation, oxidative stress, DNA damage and gene mutations.³¹⁻³³ The microenvironment of ovarian cancer contains a broad spectrum of pro-inflammatory cytokines and chemokines contributing to the mechanism.³⁸

There are many processes that can lead to inflammation and tumorigenesis and the exposure to talcum powder products is one such exposure that can strongly enhance the tumor promotion or progression as seen in in vitro and animal studies. For example, normal repeated ovulation leads to injury of ovarian epithelial cells and transformation to malignant cancer cells that can be enhanced by various factors such as talc or asbestos particles. Exposure to talcum powder products can induce the production of pro-oxidant enzymes and reduced production of antioxidant enzymes leads to malignant transformation. In support of inflammation from talcum powder products causing cancer, hysterectomy or bilateral tubal ligation, which would significantly limit ovarian exposure to inflammatory mediators, and toxins, is associated with reduced ovarian cancer risk.

Relationship Between Ovarian Cancer and Talcum Powder Products

The epidemiological evidence described in detail below demonstrates a strong and positive association between exposure to talcum powder products and ovarian cancer and that talcum powder products cause ovarian cancer. Although epidemiologic evidence alone does not provide a definitive mechanism or pathophysiological process that accounts for the increased risk, the evidence for inflammation as described above is very strong. Similarly, epidemiological evidence alone does not confirm the specific component or ingredient in talcum powder products that is responsible for its carcinogenesis. Nonetheless, several constituents within talc powder products are worth highlighting as they may be acting individually or together to create the carcinogenicity of talc powder products inasmuch as they are individually highly carcinogenic.

Why Talcum Powder Products were Initially Suspected as Causing Ovarian Cancer

In 1978 samples of commercial body powders were shown to contain asbestos silica minerals. Asbestos was a known carcinogen and about half of the powder samples contained respirable quartz, a lung carcinogen. Concerns were primarily raised that inhaled powder could cause lung scarring, lung cancer, or mesothelioma. In 1971, Henderson observed talc particles deeply embedded in ovarian cancer tissue. The authors noted the close association of talc to the asbestos group of minerals.³⁹ Further concern was raised, in 1982 when a case-control study of ovarian cancer that collected information on talcum powder use reported an increased risk with perineal dusting.⁴⁰ These findings were reported in widely circulated newspapers such as The Globe, raising concern that the powders were carcinogenic because

of the contamination with asbestos, using the relationship between asbestos and lung cancer and mesothelioma as the basis for the concern.

Carcinomic of Constituents of Talc Powder Products

There are hundreds of different constituents and ingredients within talcum powder products in addition to platy talc. Many of these are Group 1 carcinogens (such as asbestos, talc containing asbestiform fibers, heavy metals, and some fragrance chemicals) that likely contribute to the carcinogenicity of the products.

Asbestos

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibers; serpentine mineral fibers are called chrysotile, and amphibole minerals include actinolite, amosite, anthophyllite, crocidolite and tremolites. Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition. Small amounts of chrysotile (asbestos) may occur in these talc deposits^{41,42} When talc is mined it may contain asbestos fibers^{42,43} A study of 21 consumer talcum powders obtained from retail stores in 1971–1975 reported that 10 contained concentrations of asbestos fibers ranging from 0.2 to 14%.^{41,44} Because of concern that asbestos was present in talcum powder products and the known carcinogenicity of asbestos, it has been reported that voluntary guidelines were established by the cosmetic industry in 1976 to limit the content of asbestos fibers in commercial talc preparations. While currently talcum powder products are believed to free from asbestos, the data on its continued presences are strong. I have seen evidence of continued presence since 1976.⁴⁵⁻⁴⁸ For example, Longo tested approximately 50 samples that were taken between the years 1960 through 2000 and the majority of sample are positive for asbestos.⁴⁷

Asbestos is a known and potent human carcinogen. Asbestos is highly carcinogenic to the lungs, lining of the lungs, and larynx.⁴⁹ Asbestos is also highly carcinogenic to the ovaries.⁴⁹⁻⁵⁸ Women working in asbestos-manufacturing industries have an increased risk of ovarian cancer. IARC reviewed the association between asbestos exposure and ovarian cancer in 2012. To assess the relationship, IARC reviewed data primarily from large epidemiological cohort studies of women who had occupational exposure to asbestos as well case-control studies on non-occupational exposure. The context and lengths of exposures varied, along with the type of asbestos fibers to which the women were exposed and the study designs and assessments. Nonetheless, the results were consistent. Most, but not all, were statistically significant and documented a strong and compelling causal association between exposure to asbestos and ovarian cancer, largely the result of the association from cohort studies of women with substantial occupational exposures.⁵⁰⁻⁵⁴ **IARC concluded that there is sufficient evidence that asbestos is carcinogenic in humans and that asbestos causes cancer of the ovary.** This is the highest risk category.⁴⁹ IARC also concluded that this categorization applied to all forms of asbestos and to talc containing asbestiform fibers (talc in a fibrous habit or fibrous talc)). IARC also concluded that asbestos is carcinogenic based on animal studies. Camargo completed a systematic review of the relationship between women occupationally exposed to asbestos and ovarian cancer.⁵⁹ The authors found that of the 18 cohort studies

the pooled standard mortality estimate for ovarian cancer was 1.77 (95% confidence interval, 1.37-2.28). The range in reported SMR values was 1.1– 5.4 across the included cohort studies and the most common values were 2–3. This study supports IARC's conclusion that exposure to asbestos causes ovarian cancer.

IARC explicitly stated that the findings in this Monograph applied to all forms of asbestos, as well as asbestiform talc (fibrous talc).

I reviewed many publications and primary research studies, including experimental and basic science models showing molecular and genetic cancer-promoting changes to cells that occur from exposure to asbestos fibers. I also strongly conclude that asbestos causes ovarian cancer.

Talc

Talc is the primary component of talcum powder products. The chemical structures of talc and asbestos can be similar. While talc particles are usually plate-like, talc can also grow as a fiber which is similar to the group of minerals called asbestos. Both are magnesium silicate and when talc has the fibrous form it is called asbestiform because of its similarity to asbestos. The form of the talc fibers is long and thin, with parallel bundles that are easy to separate from each other, and closely resembles the physical appearance of asbestos minerals. The histologic appearances of mesothelioma and ovarian cancer are similar. The known carcinogenicity of asbestos for lung, pleural, peritoneal and ovarian cancer has led to the theory that the similarity in the fibers and the resulting cancers suggests that talc works mechanistically within the ovary to induce cancer in a way that is similar to how asbestos in the chest induces mesothelioma.

Early observations demonstrated talc particles in both malignant and normal ovaries establishing a route from the perineum to the ovary and shows that many women are exposed to talc.^{39,60} In 2006, the International Agency for Research on Cancer (IARC) reviewed the data on cosmetic (perineal) talc ("non-asbestiform") application and concluded that it is possibly carcinogenic to humans.⁶¹ This is not as strong a recommendation as they made for asbestos and ovarian cancer, but nonetheless is a strong recommendation. IARC classified genital-perineal use of talc-based powder as possibly carcinogenic. Exposure to talc particles can induce an inflammatory response, either directly at the ovary and ovary-fallopian tube juncture, causing local irritation from talc particulates or through more generalized peritoneal inflammation. The mechanism that can lead to cancer is local irritation by talc fibers that disrupts the epithelial surface, increasing rates of cell division and DNA repair that can lead to mutations. Also increased are oxidative stress and cytokine production, indicating inflammation. Fibers that are incorporated into the epithelial cells enter ovarian tissue. This inflammation initiates a series of responses, supported by research, that promote cancer. The reduction in the elevated risk of ovarian cancer from talcum powder exposure after hysterectomy or tubal ligation supports the mechanism by which local irritation and inflammation to the ovary from talc or asbestos causes an elevated cancer risk.

Heavy Metals

Talc powder products can contain Group 1 metals that are considered by IARC as carcinogenic to humans. ^{44,49}

This includes nickel compounds which IARC documents cause lung and nasal cavity and paranasal sinus cancer. (IARC100c-10, 2012). Nickel compounds “cause DNA damage, chromosomal aberrations, delayed mutagenicity and chromosomal instability ... and nickel compounds act as co-mutagens.” Talcum powder products also contain Chromium (VI) (IARC100c-9, 2012) another Group 1 carcinogen, where there is sufficient evidence in humans for carcinogenicity (to the nose and nasal sinus). The mechanism includes “DNA damage, generation of oxidative stress and aneuploidy. Talc powder products can also contain Group 2A metals that are considered probably carcinogenic to humans, such as Cobalt which can be found in talc powder products. ⁶² IARC considers Cobalt metal with tungsten carbide as probably carcinogenic to humans (Group 2A), but worth noting that a number of the IARC working group members supported an evaluation in Group 1 because they judged the epidemiological evidence to be sufficient, leading to an overall evaluation in Group 1; or they judged the mechanistic evidence to be strong enough to justify upgrading the default evaluation from 2A to 1. The majority of working group members, who supported the group 2A evaluation, cited the need for either sufficient evidence in humans or strong mechanistic evidence in exposed humans. Cobalt metal without tungsten carbide is also considered possibly carcinogenic to humans (Group 2B). Cobalt sulfate and other soluble cobalt(II) salts are possibly carcinogenic to humans (Group 2B).

Any and all of these heavy metals can cause ovarian cancer through an inflammatory mechanism

Fragrances

There are more than 150 different chemicals added to Johnson’s Baby Powder and Shower to Shower products. I reviewed the expert report from Dr. Crowley that concludes that some of these chemicals may contribute to the inflammatory response, toxicity, and potential carcinogenicity of Johnson & Johnson’s talcum powder products. I concur with his opinion. ⁶³

IV. Overview of Publications on Genital Use of Talc Powder Products and Ovarian Cancer

To understand the relationship between exposure to talcum powder products and ovarian cancer, I searched for and reviewed scientific papers on this topic. I used several searchable publication databases (Scopus, Embase, Pubmed) and manually searched the reference lists of all articles I found, including a large number of reviews. The results of my review follow the explanation of the main types of studies and articles.

Explanation of study designs and article types

Nearly all published studies that I reviewed used one of two designs: case-control and cohort. Each design has strengths and biases. The commonly held view is that cohort studies are better than case-control studies. This is a misconception thus it is worth explaining their differences. Many articles I reviewed were systematic reviews, which are also explained.

Case-control studies compare people with a condition (cases) by matching them to people with similar characteristics who do not have the condition (controls) to determine the effect of a potential disease-causing factor. They often analyze existing data retrospectively, after people have been diagnosed, and involve tens or hundreds of patients. Cohort studies compare cohorts, or groups of people, who were exposed or not exposed to a potential disease agent. They often collect data on people prospectively, before they develop a disease and track their health over time. Both case-control and cohort studies, if well done, can provide accurate and meaningful information about statistical associations. In general, however, the risk of bias is greater for case-control studies. (An example is recall bias, in which women are more likely to remember and report exposure to talc powder products after they have been diagnosed with cancer compared to women without a diagnosis, perhaps because diagnosed women heard that talc powder products is harmful and are more likely to remember talc use). Nonetheless, when studying a rare disease, the case-control design is frequently highly efficient and desirable as it allows you to assemble a much larger number of cases and can delve in great depth for particular exposures. You can identify all patients who have the outcome of interest, and then query them (and some control group) about any antecedent exposure. The identification of the control group is very important. My large, National Institutes of Health-funded study of cancer risk factors in children is employing a case-control design. This design permits us to ask very detailed questions of a small number of individuals about their various exposures.

Cohort studies potentially avoid some biases of case-control studies since exposures are prospectively assessed and quantified, that is, before disease outcomes. This design also has limitations, though. An extremely important limitation is that because cohort studies are expensive and time-consuming, they rarely focus on a single, narrowly defined question such as the association between regular use of talcum powder products and cancer. Usually, researchers investigate a broad range of questions in cohort studies, so asking patients in-depth questions about any given topic is difficult, especially since tens of thousands of patients may be surveyed on many topics. Further, in cohort studies, having comprehensive assessment of outcomes on all individuals in the cohort is extremely important. Losing patients to follow up (meaning researchers cannot contact or find records on a participant) leads to study bias. The other disadvantage of cohort studies is that a very large number of patients must be assessed over a long period of time to see who will develop a rare outcome (like ovarian cancer). Because of this, typically there will be far fewer patients with disease in a cohort study as compared with case control study (like in this case).

The small number of cohort studies I found on the relationship between talcum powder products exposure and ovarian cancer did not focus on the details of this topic. While they may have included questions about talcum powder exposure, they were not sufficiently nuanced to provide meaningful information. Thus, in most of the cohort studies I found, measurements of exposure were poor, not specific, or inaccurate. Further, several had very short follow-up periods with data or information about the time before the cancer occurred. This negates an advantage of cohort studies, which is being able to learn about exposures before the cancer, eliminating recall bias.

Systematic reviews quantitatively summarize results across multiple studies. One of the rationales of this study design is that individual studies may not have enough participants to yield meaningful results because they are too small or insufficiently powered. Combining small studies can provide more stable and reliable summary estimates of the effects of disease agents and risk factors. Further, a systematic review may be better than a single study, as it provides broader evidence of the results and includes patients from diverse settings. However, in order to statistically combine and summarize the data from different research studies into a single systematic meta-analytic review, the combined studies must ask the same research question and follow sufficiently similar and rigorous scientific methods. A meta-analysis does not compensate for gaps or flaws in an original study: Combining three poorly performed studies does not yield reliable summary estimates even though there may be three times the number of patients. Similarly, combining studies that ask different research questions (for example, assessing women of different ages for a disease in which age is an important risk factor) does not provide reliable summaries. Results from different studies often vary when the studies ask different research questions, have different criteria for including participants, or use different methods. I raise these issues to point out that systematic reviews must be read extremely carefully to ensure that their conclusions are valid.

Table of Reviewed Publications

I identified and reviewed 43 English-language publications that provided quantitative data based on epidemiological studies about the relationship between genital talcum powder exposure and ovarian cancer (Table 3). This list includes 4 cohort studies, 8 systematic meta-analytic reviews, 2 studies that pooled individual patient-level data from several research studies, and 30 case-control studies. One study contributed both the systematic review and a case control study. I also read multiple review articles that are not included in the table. The epidemiological studies were published between 1982 and 2018. I have described the results organized by study design below.

Most studies used a case-control study design with a small number using a cohort study design. Although some studies assessed powder use to any part of the body or assessed the use of talcum powder on diaphragms, condoms or sanitary napkins, the primary research question that I focused on in my review and that was assessed in all included individual research studies, was whether genital area exposure to talcum powder increases risk of epithelial ovarian cancer. Occasionally, study authors assessed combination exposures (i.e., to genitals and other body parts). These studies were included as long as genital powder use was assessed. Nearly all studies adjusted for known ovarian cancer risk factors, but those factors varied. The vast majority of studies found a positive association between any exposure to talcum powder products and cancer. However, the sample size of some studies was small and resulted in high statistical uncertainty. Because of these and other limitations, quantifying a precise association between exposure and cancer was difficult from my review of the literature. The data for some studies may have shown that effects of talcum powder exposure (measured as odds ratios, ORs) was meaningful for cancer development, but with statistical

uncertainty; whereas other studies showed the reverse results, with ORs not showing a positive association, but statistical parameters suggesting that a meaningful association was nonetheless possible because of wide confidence intervals. Therefore, I thought a more precise and careful review was called for. The number of individual women included in each study and the reported or estimated effect size for “any exposure to talc” (adjusted for other risk factors such as age) are in Table 4.

A subset of the studies quantified the *intensity (frequency)* of each woman’s exposure to talc to assess the importance of use patterns (e.g., if a single lifetime use or weekly, monthly, or daily use increased ovarian cancer risk) or *dose dependency (links between the number of exposures and cancer risk, e.g., if doubling exposure doubles risk)*. Further, a subset of studies stratified by cancer type (invasive vs. low malignant potential/borderline) and whether the risks varied by histological types including the four dominant types of serous, mucinous, clear cell, and endometrioid cancer.

Studies that provided data on the frequency of talc use and association by histologic type were included in a separate systematic meta-analytic review that I conducted as part of my review of the literature to include in this report. The reason I completed my own statistical review is further explained below.

Quantifying Exposures

A large proportion of women will have used talcum powder products, highlighting the importance of this issue. However, publications that focus on women reporting “any” genital exposure to talc (i.e., talc at any point in life and for any duration) may be too broad to provide meaningful information. For example, “any use” will include women who applied talc powder products three times over five decades and women who used talc powder products daily, whose might have had 20,000 applications and exposures in comparison to three. Defining a variable as any use is the equivalent to creating a variable of any smoking use, that combines data on individuals who tried one cigarette in their life with individuals with 50 pack years of tobacco use. Combining data on women with infrequent or sporadic exposures with data from women with frequent, sustained use leads to imprecise results, masking any causal associations. Therefore, I selected the studies for my own review that quantified the frequency of talc powder products use as having the most informative data and included them in a separate systematic review.

Summary of Data

I grouped the research studies by their study design. What follows is my review of the cohort studies, systematic review studies, pooled data studies, followed by my own review.

Cohort Studies

Four cohorts (Gertig, Gates, Houghton, Gonzalez) have been published on talcum powder products and ovarian cancer.

Cohort 1: Gertig (2000) ⁶⁴

This first cohort study assessed the relationship between perineal talc and ovarian cancer within the context of the US Nurses' Health Study, a prospective study of 121,700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. These are mostly premenopausal women. While talc exposure was not an initial part of the study, questions about talc, including measuring frequency of exposure, were added in 1982; a large subset of the cohort (78,630 women) completed these questions and were included in analyses. Among these women who were followed for 14 years, 307 were diagnosed with epithelial ovarian cancer. After adjusting for confounding variables, the *relative risk (RR)* of developing ovarian cancer (*the likelihood of ovarian cancer in talc users compared to nonusers, with higher RR meaning increased risk stronger association*) among daily users of talc was RR 1.12 (95% confidence interval [CI] 0.82, 1.55, *a measure of statistical uncertainty, with wider ranges indicating greater uncertainty*), which was not statistically significant. However, when results were classified by histologic subtype, the RR of invasive serous cancers was significantly elevated among any users of talc (RR 1.40, 95% CI 1.02, 1.9) and the RR of invasive serous cancer among daily users of talc was higher at RR 1.49 (95% CI 0.98, 2.3).

In this cohort study, the researchers assessed talc exposure before cancer diagnosis, avoiding the possibility of the recall bias of case-control studies. This was a strong strength of this study. A potential weakness was that frequency (i.e. daily) but not duration (number of years) of talc use was measured, so a clear lifetime exposure measure was missing. The researchers nonetheless quantified exposure at the time the talc questions were asked, which was probably strongly associated with prior use (i.e. an approximation on ongoing use). **This study provides strong evidence that perineal exposure to talc increases the risk of invasive serous ovarian cancer, particularly among daily users of talc, with about a 50% increased risk,** which is substantial and meaningful.

Cohort 2: Gates (2010) ²⁴

This study assessed the association between ovarian cancer risk factors and incidence of ovarian tumors by histological type using data from the US Nurses' Health Study combined with data from the Nurses' Health Study II, which included a second period of enrolling participants. Unfortunately, talc use was assessed only on the first survey and not assessed among patients enrolled in the Nurses' Health Study II. Thus, this extends the period of follow up from the initial NHS but does not include greater information about risk factors. Results were presented for any talc powder products use and not for frequency of use. **Thus, this report does not add to a meaningful assessment of the relationship between talc use and ovarian cancer because it used exactly the same patient group as Gertig (2000) but provided less information to quantify the frequency of talc use.**

Cohort 3: Houghton (2013) ⁶⁵

This study assessed perineal talc powder products use and risk of ovarian cancer in the Women's Health Initiative Observational study, in which postmenopausal women aged 50–79 were enrolled in a prospective cohort of women from 40 clinical centers across the United

States in 1993–1998. Overall, 61,576 women were included in analyses, including 429 diagnosed with ovarian cancer. Perineal powder use was assessed at the start of the study. Participants were asked if they **ever used talc powder products** on their private parts (genital areas). Those who responded yes were asked about duration (years) of use. Women were followed for a mean of 12 years and the median age of participants was 63. **Talc powder products use was associated with a 12% increase in risk of ovarian cancer after accounting for covariates** (RR 1.12, 95% CI 0.92, 1.36). When limited to women who used perineal powder for 20 years or more, the RR was 1.10 (95% CI 0.82, 1.48). When limited to serous ovarian cancer, the RR was 1.13 (95% CI 0.84, 1.51.) **The primary limitation of the study was that frequency of talc powder products use was not assessed—and thus the authors could focus only on any talcum powder use.** The imprecision in estimation of talcum powder exposure makes the results not terribly meaningful. The second limitation was the relatively short follow-up of 12 years to identify ovarian cancer diagnoses.

Cohort 4: Gonzalez (2016) ⁶⁶

The Sister Study (2003–2009) followed 50,884 women ages 35 to 75 years in the US and Puerto Rico who had a sister diagnosed with breast cancer. After excluding participants who had bilateral oophorectomies, ovarian cancer, or were lost to follow-up, 41,654 participants were included. At baseline participants were asked about douching and talc use during the previous 12 months, and during follow-up (median of 6.6 years) 154 participants reported a diagnosis of ovarian cancer. The authors computed adjusted hazard ratios (HR) and 95% confidence intervals (CI) for ovarian cancer risk using the Cox proportional hazards model. The authors found no significant association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73 CI: 0.44, 1.2). **The primary limitations of this study are that the authors combined a large number of potential talc exposures into a single category, including genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Further, the authors categorized the exposure based on the 12 months prior to enrollment as a dichotomous ever/never.** Thus not only was it an ever versus never category, the ever category was extremely broad, making the lack of association less meaningful. Further, there are several other factors that make the results questionable, including lower than expected proportion of women who report any exposure to talc powder products, and the lack of a validated approach to ascertainment of ovarian cancer.

Cohort Studies: Summary

Analyses of data from the US Nurses' Health study and the Women's Health Initiative estimated that women who report any exposure talc powder products will have a 12% increase in ovarian cancer compared to women who never report talc powder products use, although this estimate was not statistically significant. The primary limitation of this estimate is that it is based on *any talc powder products* use, which is a weak, crude predictor. Similarly, while the results from the Sisters study did not identify a significant association between talc powder products use and ovarian cancer, they too used a measure of ever use, and included a large number of different types of exposures that would not be expected to measure a single exposure. The most important and meaningful conclusion that I draw from the cohort studies

is from the Gertig 2000 study using data from the US Nurses' Health study: That women who are **daily users of talc have an approximately 50% increase (OR 1.49) in their risk of invasive serous** cancer, the most lethal and frequent type of ovarian cancer.

Systematic Reviews

I found nine systematic reviews that summarized the relationship between talc and ovarian cancer, summarized below. These reviews were completed using various subsets of the full list of publications. The systematic reviewers are presented with the most recent first, because the more recent studies tended to be more complete, comprehensive and the most methodologically rigorous.

Systematic Review 1: Penninkilampi (2018) ⁶⁷

This comprehensive systematic review of the association between any genital use of talcum powder products and ovarian cancer conducted a stratified analyses showing the association by frequency of talc use and histologic cancer subtype. The methods of the study are well described. The researchers identified studies using six electronic databases and reviewed publications with 50 or more cases of ovarian cancer. They identified 24 case-control studies describing 13,421 cases and the three cohort studies (890 cases, 181,860 person-years) described above. Any reported use of perineal talc powder products was associated with increased risk of ovarian cancer compared to no use (OR = 1.31; 95% CI 1.24, 1.39). Women with more than 3600 lifetime applications had slightly higher risks (OR = 1.42; 95% CI 1.25, 1.61). Women who reported long-term (>10 years) talc use also had an increased risk (OR 1.25; 95% CI = 1.10, 1.43). The association between any talcum powder product exposure and ovarian cancer was limited to studies that used a case-control design. The cohort studies showed an increased risk of serous invasive cancer subtypes for perineal talc use compared to no use (OR = 1.25; 95% CI = 1.01, 1.55). While serous and endometrioid cancer were associated with talcum powder products use, no association was seen with mucinous or clear cell cancers. The review authors concluded, from the data, that perineal talcum powder use and ovarian cancer were consistently associated, with a slightly higher risk in women who report greater usage. Some variation in the magnitude of the effect of talcum powder products was found when considering the study designs and ovarian cancer subtypes. Several small methodological issues are that Penniniklampi may have included some groups of patients more than once in analyses and did not include updated data or previously unpublished data available from a research consortium on ovarian cancer. However, these concerns are unlikely to have had a significant impact on their estimates.

Table 3. List of Included Studies, sorted by study design

	Study Type	Year	Author	Journal	Title
1	Cohort Study	2000	Gerting	J Natl Cancer Inst	Prospective study of talc use and ovarian cancer (in the Nurses' Health Study)
2	Cohort Study	2010	Gates	Am J Epidemiol	Risk factors for epithelial ovarian cancer by histologic type; US Nurses Health Study
3	Cohort Study	2014	Houghton	J Natl Cancer Inst	Perineal powder use and risk of ovarian cancer: Results from the Women's Health Initiative
4	Cohort Study	2016	Gonzalez	Epidemiology	Douching, talc use and risk of ovarian cancer: Results from the Sister Study
5	Systematic Rev.	1992	Harlow	Obst Gyn	Perineal exposure to talc and ovarian cancer risk
6	Systematic Rev.	1995	Gross	J Expo Anal Env Epid	A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer
7	Systematic Rev.	2003	Huncharek	Anticancer Res	Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies
8	Systematic Rev.	2007	Huncharek	Eur J Cancer Prev	Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies.
9	Systematic Rev.	2008	Langseth	J Epid Community Health	Perineal use of talc and risk of ovarian cancer.
10	Systematic Rev.	2010	IARC	IARC Monographs	IARC monographs on the evaluation of carcinogenic risks to humans: Carbon black, titanium dioxide, and talc
11	Systematic Rev.	2017	Berg	European J of Can Prev	Genital use of talc and risk of ovarian cancer: A meta-analysis
12	Systematic Rev.	2018	Penninkilampi	Epidemiology	Perineal talc use and ovarian cancer: A systematic review and meta-analysis.
13	Pooled Data	2013	Terry	Cancer Prev Res	Genital powder use and risk of ovarian cancer: a pooled analysis of 8525 cases and 9859 controls
14	Pooled Data	2016	Cramer	Epidemiology	The association between talc use and ovarian cancer- A retrospective case- control study two US states
15	Case-Control	1982	Cramer	Cancer	Ovarian cancer and talc: A case control study
16	Case-Control	1983	Hartge	JAMA	Talc and ovarian cancer
17	Case-Control	1988	Whittemore	Am J Epidemiol	Personal and environmental characteristics related to epithelial ovarian cancer. Exposure to talcum powder, tobacco, alcohol, and coffee
5	Case-Control	1989	Harlow	Am J Epidemiol	A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc
18	Case-Control	1989	Booth	BR Cancer	Risk factors for ovarian cancer: a case-control study
19	Case-Control	1992	Harlow	Obstet Gynecol	Perineal exposure to talc and ovarian cancer risk
20	Case-Control	1992	Rosenblatt	Gynecol Oncol	Mineral fiber exposure and the development of ovarian cancer
21	Case-Control	1992	Chen	Int J Epidemiol	Risk factors for epithelial ovarian cancer in Beijing, China
22	Case-Control	1993	Tzonous	Int J Cancer	Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer
23	Case-Control	1995	Purdie	Int J Cancer	Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study
24	Case-Control	1996	Shushan	Fertil Steril	Human menopausal gonadotropin and the risk of epithelial ovarian cancer
25	Case-Control	1997	Chang	Cancer	Perineal talc exposure and risk of ovarian carcinoma
26	Case-Control	1997	Cook	Am J Epidemiol	Perineal powder exposure and the risk of ovarian cancer
27	Case-Control	1998	Green	Int J Cancer	Tubal sterilization, hysterectomy and decreased risk of ovarian cancer.
28	Case-Control	1998	Godard	Am J Obstet Gynecol	Risk factors for familial and sporadic ovarian cancer among French Canadians: A case-control study
29	Case-Control	1999	Cramer	International J of Cancer	Genital talc exposure and risk of ovarian cancer
30	Case-Control	1999	Wong	Obstet Gynecol	Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study
31	Case-Control	2000	Ness	Epidemiol	Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer
32	Case-Control	2004	Pike	Fertil Steril	Hormonal factors and the risk of invasive ovarian cancer: A population based case control study
33	Case-Control	2004	Mills	Am J Epidemiol	Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California
34	Case-Control	2008	Goodman	Endocr Relat Cancer	Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk
35	Case-Control	2008	Gates	Cancer Epid Bio Prev	Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer
36	Case-Control	2008	Merritt	Int J Cancer	Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer
37	Case-Control	2009	Moorman	Am J Epidemiol	Ovarian cancer risk factors in African-American and white women
38	Case-Control	2009	Wu	Int J Cancer	Markers of inflammation and risk of ovarian cancer in Los Angeles County
39	Case-Control	2011	Rosenblatt	Gynecol Oncol	Mineral fiber exposure and the development of ovarian cancer
40	Case-Control	2012	Lo-Cignaia	Epidemiol	Aspirin, non-aspirin non-steroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer
41	Case-Control	2012	Kurta	Cancer Epid Bio Prev	Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study
42	Case-Control	2015	Wu	Cancer Epid Bio Prev	African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic whites after considering nongenetic risk factors and oophorectomy rates
43	Case-Control	2016	Schildkraut	Cancer Epid Bio Prev	Association between body powder use and ovarian cancer: the African American Cancer epidemiology Study

Table 4. List of Included Studies with Number of Cancers, Controls, and Reported Odds Ratios

	Study Type	Year	Author	Cancers	Controls or Cohort Size	Odds Ratio	95% CI
1	Cohort Study	2000	Gerting	307	78,630	1.12	(0.82,1.55)
2	Cohort Study	2010	Gates	797	108,073	1.06	(0.89, 1.28)
3	Cohort Study	2014	Houghton	427	61,576	1.12	(0.92,1.36)
4	Cohort Study	2016	Gonzalez	154	41,654	0.73	(0.44,1.2)
5	Systematic Review	1992	Harlow *	1,106	1,756	1.30	(1.1, 1.6)
6	Systematic Review	1995	Gross	1,333	2,362	1.29	(1.02, 1.63)
7	Systematic Review	2007	Huncharek	1,858	2,830	NA	NA
8	Systematic Review	2003	Huncharek	5,260	6,673	1.33	(1.16, 1.45)
9	Systematic Review	2008	Langseth			1.35	NA
10	Systematic Review	2010	IARC			1.30	
11	Systematic Review	2017	Berg	15,230	NR	1.22	(1.13, 1.30)
12	Systematic Review	2018	Penninkilampi	14,311	NR	1.31	1.24, 1.39
13	Pooled Data	2013	Terry	4,472	6,175	1.37	(1.19-1.58)
14	Pooled Data	2016	Cramer	2,041	2,100	1.38	(1.01,1.99)
15	Case-Control Study	1982	Cramer	215	215	1.58	(0.98, 2.47)
16	Case-Control Study	1983	Hartge	135	171	2.50	(0.70, 10.0)
17	Case-Control Study	1988	Whittemoore	188	539	1.45	(0.94, 2.22)
5	Case-Control Study	1989	Harlow	116	158	1.10	(0.70,2.1)
18	Case-Control Study	1989	Booth	235	451	1.30	(0.80,1.9)
19	Case-Control Study	1992	Harlow	235	239	1.80	(1.1, 3.0)
20	Case-Control Study	1992	Rosenblatt	77	46	1.70	(.70, 3.9)
21	Case-Control Study	1992	Chen	112	224	3.90	(0.9,10.6)
22	Case-Control Study	1993	Tzonous	189	200	1.05	(.28, 3.98)
23	Case-Control Study	1995	Purdie	824	860	1.27	(1.04, 1.54)
24	Case-Control Study	1996	Shushan **	200	408	2.00	NA
25	Case-Control Study	1997	Chang	367	564	1.51	(1.13,2.02)
26	Case-Control Study	1997	Cook	313	422	1.60	(0.9, 2.9)
27	Case-Control Study	1998	Green	824	855	1.30	(1.1, 1.6)
28	Case-Control Study	1998	Godard	170	170	2.49	(0.94,6.56)
29	Case-Control Study	1999	Cramer	563	523	1.60	(1.18, 2.15)
30	Case-Control Study	1999	Wong***	499	755	1.13	(0.89, 1.43)
31	Case-Control Study	2000	Ness	767	1,367	1.50	(1.1, 2.0)
32	Case-Control Study	2004	Pike				
33	Case-Control Study	2004	Mills	256	1,122	1.74	(1.14, 2.64)
34	Case-Control Study	2008	Goodman	367	602	0.99	(.70, 1.41)
35	Case-Control Study	2008	Gates			1.41	(1.14, 1.76)
36	Case-Control Study	2008	Merritt	1,576	1,509	1.34	(1.06, 1.68)
37	Case-Control Study	2009	Moorman	1,086	1,057	1.37	(1.05, 1.80)
38	Case-Control Study	2009	Wu	609	688	2.08	((1.34 3.23)
39	Case-Control Study	2011	Rosenblatt	812	1,313	1.13	(0.93,1.36)
40	Case-Control Study	2012	Lo-Cignaie	902	1,802	1.34	(1.07,1.66)
41	Case-Control Study	2012	Kurta	902	1,802	1.41	(1.16, 1.69)
42	Case-Control Study	2015	Wu	1,701	2,391	1.46	(1.27,1.69)
43	Case-Control Study	2016	Schildkraut	584	745	1.71	(1.26, 2.33)

Odds ratio, likelihood (odds) that an outcome will occur because of a particular exposure compared to the likelihood it will occur without the exposure. 95% CI, 95% confidence interval, a measure of statistical uncertainty that says with about 95% of the time that the true value is within the range of numbers. The wider the range, the higher the uncertainty. NR, not reported.

* crude unadjusted estimate

** approximate, unadjusted estimate

*** assessed perineal or thigh use, and controls all have cancer

Berge (2018) ⁶⁸

This large, comprehensive systematic review of the association between genital use of talc powder products and ovarian cancer also had well-described methods. Berge reviewed and abstracted data for 27 publications and reported an overall summary estimate of the association between talc exposure and ovarian cancer. For six of the reviewed studies, Berge included data published in a pooled data analysis, from Terry ⁶⁹ described below) that had not been previously included in the original publications. Overall, data on 15,230 women with ovarian cancer were analyzed (a number that is incorrectly reported in the paper). This is slightly higher than the number included in Penninkilampi because of the additional patients from the Terry publication. The summary estimate for risk of ovarian cancer for women who ever used genital talc was RR 1.22 (95% CI 1.13, 1.30). When stratified by histologic type, serous carcinoma was the only type with a significant association to talc use (RR 1.24, 95% CI 1.15, 1.34). There was no difference in risk when tumors were categorized as invasive versus borderline.

To assess relationships among ovarian cancer and intensity and duration of use, these measures were analyzed separately rather than as a combined measure that would give an estimate of the total number of exposures; the analyses did not demonstrate a significant dose response. Importantly, these measures were assessed only in five studies with the results on frequency of use presented as increased risk per additional day per week of talc use, which assumes a very linear association. I was not able to identify the original studies used in the review that reported the results with this level of granularity. Because of the small number of studies, the results (3% increase in risk per additional day of talc used, with high statistical uncertainty) were not surprising.

The authors also stratified the results by the study design (as did Penninkilampi) and found that the association between talc exposure and ovarian cancer was significant only for the case-control studies, although, as above, the cohort studies had the weakest definition of exposure. The primary limitation of the review is defining exposure as ever having used talc. As described above, this is a broad, vague definition that probably dilutes any estimated association, as it includes both women with trivial use and with regular use. A second limitation is that the included studies adjusted for a variety of covariates although this is unavoidable in this type of summary. The large difference in general between adjusted and crude results emphasizes the importance of adjustments when estimating particular risk.

Langseth (2008) ⁷⁰

This systematic review of the association between genital use of talc powder products and ovarian cancer included 21 publications. The overall pooled odds of cancer were OR 1.35 across all studies. Several authors of this systematic review were involved in an IARC report on talc exposure. They analyzed a subset of eight studies used in the IARC report that were considered to be the most informative for estimating ovarian cancer risk. Analysis of these more relevant, higher quality studies, produced an increased ovarian cancer risk of 30 to 60% (presumably OR 1.3–1.6) associated with talcum powder use. This subset analysis did not document a dose response or assess associations by cancer types.

Huncharek (2007) ⁷¹

Huncharek summarized the results of nine studies that reported on the association between talc used on contraceptive diaphragms and ovarian cancer. No data on perineal talc exposure were analyzed and the data are not included herein. Of note, the reported methodological details suggest a very poorly designed and conducted study. Some of the included papers do not even mention talcum powder products used with diaphragms. This systematic review is poor quality.

IARC (2006) ⁶²

Beginning in 1969 the International Agency for Research on Cancer (IARC) began a program to critically review the data on the carcinogenic risk of chemicals to humans. They subsequently expanded their reviews to include evaluation of carcinogenic risks associated with a range of exposures (including risks associated with biological and physical agents, lifestyle factors, complex mixtures of exposures, occupations, etc.) The purpose of the IARC program is to elaborate and publish detailed monographs including critical review of data, to evaluate human risks, and to indicate where uncertainty exists and where additional data are needed. They also give an overall assessment of the strength of the associations. It is worth noting that the individuals who contribute to IARC reports (the Working Group) include extremely knowledgeable and unbiased scientists who have specific content expertise and who have no apparent conflicts of interest. Invited specialists and representatives from international health agencies are brought in to supplement the scientific experts. In their evaluation, they heavily weight whether data support a conclusion of causality. They score evidenced into four categories, ranging from a) evidenced suggesting lack of carcinogenicity; b) inadequate evidence of carcinogenicity c) limited evidence of carcinogenicity and d) sufficient evidence of carcinogenicity. Category c is used when there is possibly carcinogenicity, and this category is not used lightly. An exposure meets category c if there is a positive association between observed exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance of bias or confounding could not be ruled out. They further categorize agents into 3 groups: Group 1, corresponding to d above (sufficient evidence), the agent is carcinogenic to humans; Group 2, which includes 2A (the agent is probably carcinogenic) and 2B: the agent is possibly carcinogenic to humans. A review focused on the risks associated with carbon black, titanium oxide and talc was published in 2006. The review included a detailed review of the individual studies examining perineal talc use as a risk factor for cancer. IARC concluded that perineal use of talc-based body powder is possibly carcinogenic to humans (Group 2B)

Huncharek (2003) ⁷²

This review of 16 studies assessed the relationship between genital exposure to talc and ovarian cancer using data for 5260 women with cancer and 6673 controls. The pooled OR for ever being exposed to perineal talc powder products was 1.33 (95% CI 1.16, 1.45). Small differences were observed in the estimated ORs by whether controls in the case-control studies were from hospital populations (OR 1.19, 95% CI 0.99, 1.4), or the general population (OR 1.38, 95% CI 1.25, 1.52). I believe these differences are small. In general, in case-control

studies, population controls are likely more relevant and valid. However, as with several of the other reviews, talcum powder exposure was assessed as any exposure rather than quantifying by intensity. No stratification by tumor subtype or invasiveness was performed.

Gross (1995) ⁷³

Gross reviewed 10 studies on the association between talc exposure and ovarian cancer using data on 1333 women with cancer and 2362 without cancer. To summarize the RR of malignant epithelial cancer types due to any exposure to talc, adjusting for ovarian cancer risk factors, the authors combined results from five studies for OR 1.29 (95% CI 1.02, 1.63). For an analysis of all cancers (borderline and invasive), they included data from seven studies for a similar OR of 1.31 (95% CI 1.08, 1.58). Notably, the authors did not provide any methodological details of how they identified, assessed, and combined studies, making the results difficult to fully interpret. As with several of the other reviews, they assessed any exposure to talc.

Harlow (1992) ⁷⁴

Harlow reviewed five previously published studies and summarized an OR, not adjusted for confounding factors, and added his own data for a crude estimated OR of 1.3 (95% CI 1.1, 1.6). Unfortunately, no methodological details were provided on how studies were identified, assessed, and combined or how exposure was defined, making the results difficult to fully interpret. Further, only the combined, estimated, non-adjusted crude OR was reported. Of note, the results of the five published studies used in the review (in contrast to the summary) are well described and of good methodological quality.

Systematic Reviews: Summary

The systematic reviews provide a remarkably consistent estimate of an approximately 30% increase in the risk of ovarian cancer associated with any talc powder products use. The studies summarized in the systematic reviews reported consistent results with little variability and closely overlapping estimates for ovarian cancer risk due to talc use. Further, the reviews suggest that the risks are greater for invasive serous cancer. I believe Penninkilampi provides a comprehensive and high quality review and his estimate is that women who regularly use talc powder products, defined as >3600 lifetime applications, have a 40% increased risk of ovarian cancer compared to women with no regular talc power product use. The association was significant for serous cancers.

While the methodological approaches of these systematic reviews were generally valid, I believe they all shared the weakness of focusing on any talcum powder use rather than daily talcum powder use, and this motivated my own review (below).

Pooled Data

Two large studies pooled data from several studies. They are worth describing because of their larger sample size and strong methodology in comparison to the individual case-control studies.

Pooled Data 1: Terry (2013)⁶⁹

This report pooled data on ovarian cancer patients from a national research consortium and assessed the relationship between talc powder products exposure and ovarian cancer by histologic subtype and invasiveness. Data were from eight case-controlled studies and importantly included previously unpublished data. The authors tried to unify definitions across the studies, but the definitions nonetheless varied widely. The prevalence of genital powder use in the controls varied widely across participating study sites, ranging from 15%–45%, suggesting either large variations in the underlying populations or, probably more likely, variation in the definition of powder use that led to these differences.

The data were for a total of 8525 cases and 9859 controls in the primary analysis. The authors found that **genital talcum powder use was associated with an approximately 24% increased risk of epithelial ovarian cancer (OR 1.24, 95% CI 1.15, 1.33)**. When stratified by cancer type, the risk was increased for all cancers except mucinous cancer. Risks were approximately equally elevated for invasive and borderline tumors. They used a subset of patient data to determine RR of ovarian cancer for the highest talcum powder users, measured as cumulative lifetime perineal applications (defined as applications per month and months of the year). They also considered age (inclusion in the highest user group required more use at age 70 than age 40) and assessed risk of cancer among the highest users. **The odds of cancer in the highest talc exposure category was higher than for women who ever used talc (OR 1.37, 95% CI 1.19, 1.58)**. A significant dose response was seen when data on all patients were analyzed, with greater exposure leading to greater risk.

Pooled Data 2: Cramer (2016)⁷⁵

Cramer conducted several case-control studies on the relationship between genital talc powder use and ovarian cancer. He pooled data from a large number of these studies, described as reflecting study enrollment in 1992–1997, 1998–2002, and 2003–2008. This publication reports the analysis of pooled data from these separate enrollment phases and a more detailed characterization of those data. Cases were women who resided in Eastern Massachusetts and New Hampshire diagnosed with epithelial ovarian cancer between the ages of 18 and 80. Controls were women identified through random-digit dialing, driver's license lists and town resident lists. Women were interviewed in person, and details of talc use were elicited including the number of applications per month (allowing assessment of frequency of use), timing of use, and lifetime exposures. These descriptions gave far greater detail than most other reports and are thus an important contribution to the field. Further, more demographic and clinical history were obtained and described in these enrollments than for other reviewed studies. This report gave associations from pooled data for 2041 cases and 2100 controls. The larger size of the population, unified variables, and greater detail about cases and controls allowed a larger number of stratifications than other studies.

Overall, genital talc use was associated with an OR of 1.33 (95% CI 1.16, 1.52). An important observation was that risk decreased with time since last use. Thus, how often women regularly used talcum powder (daily, or weekly or monthly) was meaningful for predicting ovarian cancer risk, but not if the women had not used talcum powder for 5 or more years.

Women who reported using talcum powder daily (>30 applications per month) had an OR of 1.46 (95% CI 1.2, 1.78). Of note, among women in the ovarian cancer case group who used talcum powder, daily was the most commonly reported frequency of use. **When analysis used data on women who reported their total number of talcum powder applications, those in the highest group category (>7200 lifetime applications, the equivalent of 20 years of daily application) had an OR for ovarian cancer of 1.49 (95% CI 1.06, 2.1).**

Cramer conducted detailed analysis of factors that could influence/interact with the association between talcum powder and ovarian cancer. Some of the results are quite striking. First, a very strong interaction with race was noted. **African-American women seem to be at a particularly elevated risk of ovarian cancer following talcum powder exposure (OR 5.08, 95% CI 1.32, 19.6) compared with white women (OR 1.35, 95% CI 1.17, 1.55).** This finding calls for greater research given the higher incidence, and poorer outcomes among African American women. Asian women seem to be at reduced risk (OR 0.04, 95% CI 0.01, 0.34). **Analysis showed a strong relationship with menopausal status and use of hormone replacement therapy.** ORs were significantly increased in premenopausal women (OR 1.41, 95% CI 1.13, 1.75) and **postmenopausal women who used hormone treatment (OR 2.21, 95% CI 1.63, 3.0).** Postmenopausal women who did not use hormone therapy were not at increased risk of ovarian cancer (OR 1.0, 0.68, 1.49). **Interestingly, the risk of ovarian cancer among postmenopausal hormone-treatment users was elevated only if they used hormones before hysterectomy and tubal ligation but risk was substantial (OR 3.49, 95% CI 1.39, 8.75) if talcum powder was used before these surgeries (OR 5.85, 95% CI 2.89, 11.9) compared to talcum powder use both before and after surgery.**

These findings merit further assessment in other populations but raise the possibility that estrogen is important in ovarian carcinogenesis. The authors also stratified analyses by histologic type and found that the relationship between ovarian cancer and frequency of talcum powder use was significantly elevated for invasive and borderline serous cancer and invasive endometrioid cancer, but not for mucinous, clear cell or mucinous borderline cancer. **Among the most frequent users of talc the adjusted OR for invasive serous cancer is 1.54 (95% CI 1.15, 2.07).** This relationship was even stronger among premenopausal women (OR 1.85, 95% CI 1.21, 2.8) compared to postmenopausal women (OR 1.33, 95% CI 0.96, 1.85).

Pooled Data of Case-Control Studies: Summary

The increased risk of ovarian cancer associated with talc use was estimated at around 40% across these studies. The increased risk for serous cancer was even higher at 50%.

Case-Control Trials

A large number of case-control studies are published—too many to dedicate a paragraph to summarizing the methods of each.

21,24,36,40,74,76-99

I carefully read and abstracted data from each study. Without assessing the quality of the case-control studies, I included them in a table and sorted them by size of the reported effect

of talc on ovarian cancer risk. It's a way to get an overview of what they report – and Viewing them in this way is easy to see the general direction of the effect. All but two demonstrate a positive association ($OR > 1$) between any talc powder products use and ovarian cancer, with ORs ranging from 0.73–3.9 across studies, Table 5 .

Table 5: List of Case-Control Studies Sorted by Estimated Effect Size (Odds Ratio)

Year	First author			Odds ratio	Confidence interval
	2008	Goodman	367	602	0.99 (.70, 1.41)
1993	Tzonous	189	200	1.05	(.28, 3.98)
1989	Harlow	116	158	1.10	(0.70,2.1)
1999	Wong*	499	755	1.13	(0.89, 1.43)
2011	Rosenblatt	812	1313	1.13	(0.93,1.36)
1995	Purdie	824	860	1.27	(1.04, 1.54)
1989	Booth	235	451	1.30	(0.80,1.9)
1998	Green	824	855	1.30	(1.1, 1.6)
2008	Merritt	1576	1509	1.34	(1.06, 1.68)
2012	Lo-Cignaia	902	1802	1.34	(1.07,1.66)
2009	Moorman	1086	1057	1.37	(1.05, 1.80)
2008	Gates			1.41	(1.14, 1.76)
2012	Kurta	902	1802	1.41	(1.16, 1.69)
1988	Whittemore	188	539	1.45	(0.94, 2.22)
2015	Wu	1701	2391	1.46	(1.27,1.69)
2000	Ness	767	1367	1.50	(1.1, 2.0)
1997	Chang	367	564	1.51	(1.13,2.02)
1982	Cramer	215	215	1.58	(0.98, 2.47)
1997	Cook	313	422	1.60	(0.9, 2.9)
1999	Cramer	563	523	1.60	(1.18, 2.15)
1992	Rosenblatt	77	46	1.70	(.70, 3.9)
2016	Schildkraut	584	745	1.71	(1.26, 2.33)
2004	Mills	256	1122	1.74	(1.14, 2.64)
1992	Harlow	235	239	1.80	(1.1, 3.0)
1996	Shushan **	200	408	2.00	NA
2009	Wu	609	688	2.08	((1.34 3.23)
1998	Godard	170	170	2.49	(0.94,6.56)
1983	Hartge	135	171	2.50	(0.70, 10.0)
1992	Chen	112	224	3.90	(0.9,10.6)
2004	Pike			NA	

V. Rationale for and Explanation of the New Systematic Review

In previous systematic reviews that I have conducted, I have obtained the most meaningful and consistent results by narrowly defining the research topic of the review, including only studies that provide data on this narrow topic in a well-defined population and stratifying my analysis of the studies' results by relevant factors such as age or race/ethnicity. The benefit of this approach is more accurate, precise, and meaningful results, while the potential tradeoff is a reduction in general applicability of the results, because many studies may be excluded for inadequate data. I believe greater accuracy is more important because I want to be certain about the data I am describing. For example, when I conducted a systematic review on the use of transvaginal ultrasound as a diagnostic test for endometrial cancer, I initially stratified

the results by patient use of hormone therapy. The reviewed studies had consistent results, but only if profoundly different diagnostic criteria were applied for women who did and did not use hormone therapy. For this reason, I completed one review on hormone users and another on non-users. In this case, I had sufficient data to assess both groups.

In this review on talcum powder use, I had sufficient data to summarize results for regular users of talcum powder (as close to daily but reflecting use of talc powder products several times per week) and risks of serous cancer; I did not have sufficient data to summarize results for occasional users or risk of other cancer types. I believe the most important research question to answer in this review is whether regular exposure to talcum powder is associated with ovarian cancer. I want to point out that this does not mean that other uses (i.e. less than approximate daily use) does not cause ovarian cancer, nor that talc powder products does not cause other types types of ovarian cancer (e.g. endometrioid cancer). Thus, for the systematic review below of case-control studies on the relationship between perineal exposure to talcum powder products and ovarian cancer, I focused on whether regular use of perineal (genital) talc increases the risk of the ovarian cancer. When possible, I focused on the most common and serious type, invasive serous ovarian cancer.

VI. New Systematic Review of Literature Quantifying Association Between Regular Frequent Genital (Perineal) Talcum Powder Products Application and Ovarian Epithelial Cancer Risk with A Focus on Invasive Serous Cancer.

Literature Search

I performed a literature search to identify primary research studies (not reviews) that included patient-level data on the association between talc and ovarian cancer. The literature search was performed in the Medline, Embase, and Scopus databases using keywords “ovarian cancer,” “talc,” “perineal powder” and “genital powder.” Abstracts of resulting publications were reviewed to identify if they addressed the topic and included data. Only English-language articles were reviewed. The references of identified articles and reviews were scanned to identify additional publications. Review articles, editorials, letters to the editor were excluded.

Article Selection

Articles were included based on relevance to the question: **Does the regular (as close to approximately daily) use of genital (perineal) talcum powder increase invasive epithelial ovarian cancer?** Because daily use was the most dominant use category, when studies stratified their results into quartiles of use, or lifetime applications, I included the highest use category that had a reasonable number of data points to reflect daily use. Wherever possible, data on invasive serous cancer were abstracted separately. When I found duplicate reports on the same patient group, the largest and most detailed publication was included. This usually meant the most recent publication, but not always. An important caveat is that I could not always identify duplicative results. I included data from the Terry 2013 pooled data study because it included new data from previous studies. I also included data from the Cramer

2016 pooled analysis and earlier publications with duplicative patients were not included. But I calculated the results both including and excluding these studies.

Exclusion

Studies were not included if they reported only crude ORs unadjusted for confounding factors. A few studies were excluded because, the research methods were poorly defined, even though they reported on women who frequently used talcum powder. Studies that asked participants a single question about ever use of talcum powder, without further quantification of exposure, were not included in the summary.

Defining Talcum Powder Products Use

Regular use was defined ideally as daily or at least more than 3 uses per week. I also accepted studies that defined use as “regular” where the description made it clear that this was regular use. Studies that reported “regular use” but defined it as use of less than this frequency, were not included. Regular use was selected to differentiate occasional use (which may include one-time or infrequent use or use during only a particular time of a woman’s menstrual cycle) from sustained regular use. Studies that asked participants a single question about ever use of talc, without further quantification of exposure, were not included in the summary. For example, Purdie reported that 52–57% of women reported ever using talc without further quantification and was not included. Several studies asked about *regular use* defined as at least once a month. These studies were not included unless they further characterized women into different categories of use; if so, I included data for women in the highest use category as long as this was group was large enough to be meaningful. When studies asked about ever use but defined use and stratified results by use, I included any data that may have reflected daily use. This measure of regular use is imprecise but is more accurate and meaningful than evaluating talcum powder exposure as any use.

Stratification of Analyses: Focus on a Single Histologic Type Where Possible

My review focused on invasive serous cancer where possible, but also included all invasive cancer. The decision to focus on a single histologic cancer type was in part because ovarian cancers include a broad range of types and association of talc and ovarian cancer might differ by type. I chose serous cancers because they are most common invasive ovarian cancer type. Importantly, serous ovarian cancer is the only histologic type for which most individual research studies accumulated sufficient cases for valid statistical analysis. This cancer type also has the least uncertainty in pathological diagnosis (see Section III, Histologic Types). Further and most importantly, serous ovarian cancer is the most aggressive histologic type, so identifying causal factors is important. Finally, I focused on invasive cancer (as opposed to borderline cancer) because the risk of death from invasive serous tumors is far higher than for noninvasive types, with growing consensus that borderline tumors may not be malignant.

Type of Exposures

Studies were included if they reported on perineal exposure (rather than exposure through sanitary napkins, diaphragms, or condoms) as this is the most common exposure type and is

likely to reflect the most consistent exposure. I did not exclude studies if they reported combined use, as long as the exposure included perineal use.

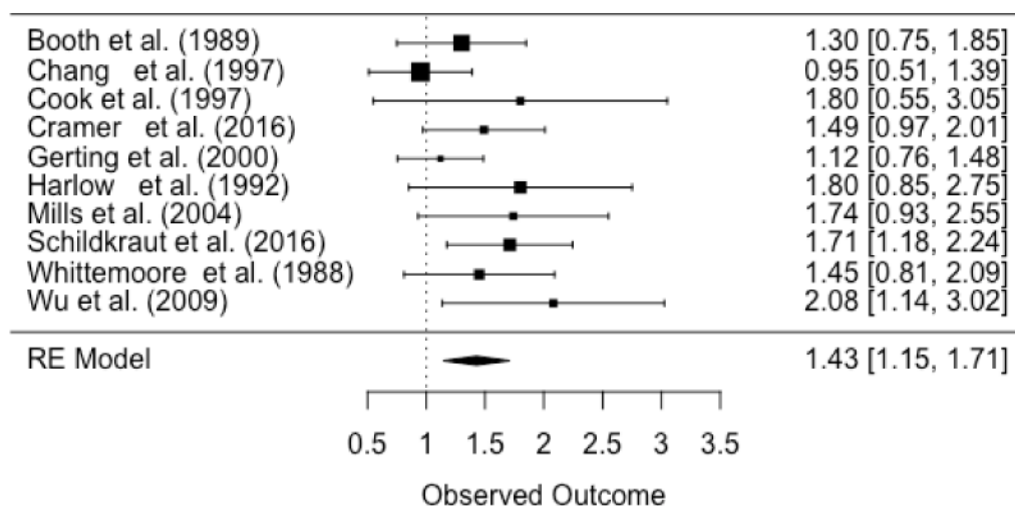
Statistical Analysis

Two individuals (Smith-Bindman and a consultant biostatistician) reviewed an abstracted data from each publication. Differences were resolved by consensus. The focus of the review was on quantifying the association between regular talcum powder products use and ovarian cancer, with a sub analysis on serous cancer and invasive cancer. Meta-analysis was performed using the metafor package in R (Version 3.5.1). The rma function was used to apply linear mixed effects models to study results and calculate summary statistics on effect size. Due to varying amounts and types of available data from each included publication, adjusted odds ratios (OR) and standard errors were used as the model inputs. Standard error (SE) was estimated using the relationship: 95% confidence interval = Effect size \pm 1.96*SE, assuming a roughly normal distribution of data and roughly symmetrical upper and lower confidence interval bounds. Incorporating adjusted ORs and SE into models in this way provides the added benefit of allowing model use of covariate-adjusted data (versus crude OR data). Weighting was done based on estimates of inverse variance. Study result heterogeneity was estimated based on maximum likelihood methods and was summarized via an I² statistic and associated p-value. The decision to include results from the cohort study by Gertig and colleagues (2000), which reported relative risk (RR), was based on the estimation that the RR value was only nominally different from the OR, a safe assumption in a study sample where less than 0.4% of the cohort developed the condition-of-interest.

Results

Overall 10 studies reported on daily talc powder products use and the risk of ovarian cancer. These studies were homogenous, and the odds of ovarian cancer associated with regular use was 1.43 (95% CI 1.15 1.71). The included studies with associated point estimates are shown in a Forrest Plot in Figure 2

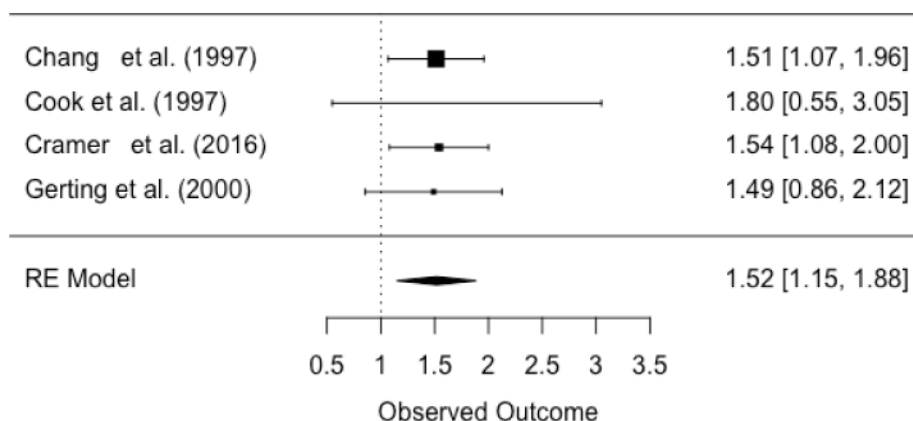
Figure 2. Forrest plot showing odds of ovarian cancer associated with regular use of talcum powder products.



The primary analysis of this excluded Terry, but the results were nearly identical if Terry was included

There were studies reported on regular talcum powder use and invasive serous cancer (or all invasive cancer if serous not reported) These studies were homogenous. The odds of invasive serous cancer associated with regular use was 1.52 (95% CI 1.15, 1.88). The results were similar when assessing the odds of all serous cancer.

Figure 3 Forrest plot showing odds of ovarian cancer associated with regular use of talcum powder products and invasive serous cancer.



New Systematic Meta-Analytic Review: Summary

The results of my systematic review of case-control studies on talcum powder use and ovarian cancer risk were consistent and indicate a **50% increase in risk of serous invasive cancer related to routine talcum powder exposure compared to no exposure**. This review had limitations including that study results were self-reported. I tried to be consistent in defining exposure, but this factor was subjectively determined by the individual studies. I tried to eliminate overlap of participant populations used in the included studies, but some patients may have contributed data to more than one study.

Overall Summary of the Epidemiology Data Describing the Association Between Talcum Powder Products and Serous Ovarian Cancer

I conclude, based on the review of the available primary studies, systematic reviews and my own quantitative review, that regular exposure to talcum powder products increases ovarian cancer risk by around 50%. The existing systematic reviews (in particular Penninkilampi and Berge) also concluded a significant increase in ovarian cancer risk following talcum powder exposure.

VII. Other Relevant Factors

Research Supporting Talcum Association with Ovarian Cancer: Transit to Ovary and Risk Reduction on Interruption

Evidence from relevant studies is clear that talcum powder particles applied to the genital region will ascend through the vagina and fallopian tubes and enter the pelvic cavity, reaching fallopian tubes and ovaries. In humans, this route has been established experimentally by labelling inert particles, applying them to the perineum just prior to planned hysterectomy, and then recovering them from the fallopian tubes following surgery. [Egli Fertil Stwriil 1961]

Further, talc particles have been found in normal and malignant ovarian tissue. Henderson found that in 10 of 13 tested epithelial ovarian cancer tumors, 75% had talc embedded in the tissue. This result confirms that talc reached to the areas with cancerous tissue, but not that it caused the cancer. Histological evaluation of ovaries removed because of ovarian cancer or benign conditions have identified both talc particles and asbestos fibers in the ovarian tissue, further supporting that particles applied to the perineum reach the ovaries.^{60,100} Heller found that in all women in a study who were having ovaries removed for benign ovarian growth had talc in their ovaries. These results confirm that talcum powder applied to the perineum may be absorbed into the vagina and migrate or be transported to the tubes and ovaries.¹⁰¹⁻¹⁰⁴ In 1967, Graham and Graham demonstrated that intraperitoneal application of asbestos in guinea pigs and rats results in overgrowth of ovarian epithelial cells comparable to the histologic changes in epithelial ovarian tumors in women. The greater frequency at which talc particles are discovered in ovarian cancerous tissue than in normal ovarian tissue further supports that these particles may be causing cancer.

Several epidemiological studies evaluated the risk of ovarian cancer associated with talcum powder products before and after women had tubal ligation or hysterectomy, which surgically removes the route by which talc reaches the ovaries. The studies strongly suggest that the increased risk of ovarian cancer associated with talcum powder products use is reduced or eliminated after tubal ligation or hysterectomy. The results support that the risk from talcum powder products is elevated when women have an open pathway from the perineum to the ovary that enables powder components to reach the ovaries via unobstructed fallopian tubes., The collective results demonstrate that talcum powder products are carcinogenic through direct transport/migration to the fallopian tubes and ovaries.

Variation in Risk when Talc Use is Discontinued

Several studies showed that the risk of ovarian cancer associated with talc powder products decreases as the time from discontinuation of powder use increases. For example, Cramer found an elevated risk of ovarian cancer with talc powder products use and the risk decreased as time since last use increased.⁷⁵

VIII. Consideration of Causality of Talc Powder Products and Ovarian Cancer : Bradford Hill Analysis

Causality is easiest to determine in studies such as randomized controlled trial, in which participants are randomized to receive or not receive a treatment, then their health is followed to see their response. However, people cannot ethically be randomized to be exposed to a potentially cancer-causing agent. Therefore, when assessing risk factors for cancer, the Bradford Hill Factors are often used. They provide a framework for assessing the weight of evidence to help decide if causality is likely, given a particular association, such as between talcum powder and ovarian cancer. The guidelines are imperfect and provide a framework as compared with an absolute set of criteria.

I address each of the Bradford Hill factors below, with my understanding of how the evidence of talcum powder products exposure supports or refutes causality. While the Bradford Hill Factors include nine aspects of association, they should not be used as a checklist for causation. Instead, they can help interpret associations and aid in inferring causality. For each factor, I have highlighted why I believe this factor is more or less important.

A) Strength of Association

It is frequently argued that the larger an apparent association, the more likely the association is to be real (causal) and important for epidemiological assessment. This would suggest that an OR of 2.0 is more likely to indicate causality and importance than an OR of 1.5. While this is often argued, I do not believe this is necessarily the case. If a risk factor increases the risk of disease by 50%, and the exposure is common, it will have a far greater impact on a number of people, in comparison to a rare exposure that has a higher associated OR. And if the association is truly one that increases risk by 50%, then this is the magnitude of the association that will be detected. It is not intuitive that if an exposure increases a risk by 50%, this difference is not discoverable compared with an exposure that increases risk by 100%. A larger association between exposure and disease may be easier to identify, but I do not believe it is more likely to indicate causality or importance.

As an example, Table 6 shows an overview of the relationship between bladder cancer and two of its known risk factors; occupational industrial chemicals and smoking. Several industrial chemicals such as 2-naphthylamine are strongly associated with bladder cancer risk. In 1954, Case et al. reported a 200-fold increased bladder cancer risk for workers exposed to 2-naphthylamine. In cohort studies of rubber industry workers, elevated standardized mortality ratios (SMRs) as high as 253 (95% CI 93, 551) were reported. Use of some of these chemicals are now prohibited in Europe and their use is regulated in the United States because they cause cancer. (OSHA, 2011).

Cigarette smoking is also a known bladder cancer risk factor. However, the RR for smoking and bladder cancer is around 3, and therefore about 100 times lower than the RR for exposure to industrial chemicals. Yet bladder cancer is the second most common cancer attributed to smoking in the United States. It impacts a very large number of individuals. Of the 70,000 cases of bladder cancer diagnosed each year, as many as 60% are estimated as attributable to smoking.

Using the RR magnitude to quantify the “importance” of these two risk factors, industrial chemicals and smoking, would be misleading. Smoking will result in far more cancers than industrial chemicals, even though the RR is much lower. In the crude data in Table 6, of the approximately 70,000 bladder cancers diagnosed annually in the United States, 50,000 are thought to result from cigarettes while fewer than 1000 result from occupational exposures. A 50% reduction in smoking exposure will save 25,000 men from getting bladder cancer. Reducing industrial chemical exposures will saving around 500 men from getting bladder cancer. Thus, any impact on reducing known exposures for bladder cancer has the potential to be around 50 times more impactful if directed at smoking.

Table 6. An example showing the number of individuals who might be impacted through exposure to an occupational chemical that leads to bladder cancer as opposed to smoking.

	Occupational Exposure	
	2-naphthylamine	Smoking
Estimated odds ratio associated with exposure	200	3
Number of individuals exposed annually	10,000	50,000,000
Bladder cancers due to exposure annually	1000	50,000
Impact on number of cancers diagnosed annual if exposure reduced by 50%	500	25,000

The bladder cancer example highlights that a factor that increases risk by 50% will have an enormous impact on population mortality if the exposure is common or if the cancer is particularly lethal. This is certainly the case for talcum powder products, which are used by as many as half of all women in the U.S. Women’s use of talcum powder products is so widespread that even a relatively modest increase in risk would pose a sizeable health risk to the population. Further, a 50% risk increase is particularly important for ovarian cancer, which has a high mortality rate, with rare early detection.

Defining a “strong” association is critical for assessing potentially causal relationships. A current concept in epidemiology is that considerations about whether a factor causes a disease should weigh statistical validity and significance and the multiple factors that influence the disease. Thus, assessing *strength of association* when inferring causality requires examining underlying research and analytic methods, comparing the weight of evidence in the literature, and considering other contextual factors. The data supporting the causality of talcum powder products exposure for ovarian cancer is extremely strong.

Using the existing evidence, I reviewed and assembled for this report, I estimated how many ovarian cancers that occur each year in the United States are likely to be caused by exposure to talcum powder products in comparison to other risk factors for ovarian cancer, Table 7. This is a relatively simple analysis, but nonetheless is informative. The total number of ovarian cancers that are estimated to occur in the US annually is 22,240, and these will occur among

the 50.8 percent of the U.S. population of 311 million who are women. Of these ovarian cancer cases, approximately half (11,120) will reflect invasive serous carcinoma. For the purpose of this simple analysis, I have assumed that the elevation in ovarian cancer risk associated with talcum powder product exposures occurs only with invasive serous carcinoma. This is not true, but the data are the most certain for these cancer and this is a conservative assumption (meaning the true number of cancer and proportion of cancers caused by talcum powder product users will be even higher than my calculation). A proportion of ovarian cancers will occur among women who regularly use talcum powder products, and the remainder will occur in women who do not regularly use talcum powder products. If we estimate that women who use talcum powder products regularly have a 50% elevated risk of invasive serious cancer and we estimate the number of women who are exposed to daily talcum powder products is between 10% and 30% (this proportion is fewer than ever users of talcum powder products), then between 1,589 and 4,351 women will be diagnosed each year with invasive serous cancer caused by the exposures, reflecting between 14% and 39% of all invasive serous cancers and reflecting between 7% - 20% of all ovarian cancer diagnosed each year. This is a tremendous risk. This is a very large number of cancers to be caused by a product that provides no medical benefit. This Bradford Hill Factor of the Strength of the association is important and is met.

Table 7 An estimate of the number of ovarian cancers and invasive serous cancers caused by regular use of perineal talc powder products.

Proportion of women who regularly use Talcum powder products	Annual Invasive Serous Cancer in Women Exposed to Talcum Powder Products	Annual Invasive Serous Cancer in Women Not Exposed to Talcum Powder Products	% Invasive Serous Cancer in Women Exposed to Talcum Powder Products	% of all ovarian Cancer in Women Exposed to Talcum Powder Products
10%	1,589	9,531	0.14	0.07
20%	3,033	8,087	0.27	0.14
30%	4,351	6,769	0.39	0.20

B) Consistency of Associations in Different Populations and Studies

Another consideration for association and causality is consistency of the data. The data on the association between genital talc and ovarian cancer are highly consistent. The relative stability in the estimated increase in the risk of ovarian cancer associated with talc powder products use (50% increase for regular users of talcum powder and serous cancers; around 40% increase for all epithelial ovarian cancer and regular users of talcum powder products), as assessed across time and in diverse populations with diverse study designs, strongly argues that the causal association is real and satisfies the Bradford Hill guideline for consistency of associations across populations and studies.

C) Specificity Between Cause and Effect

The Bradford Hill factors suggest that associations are more likely to be causal when an exposure causes only one disease. While some examples of highly specific exposures and outcomes exist, many exposures and health concerns involve complex chemical mixtures and low-dose environmental and occupational exposures complicated by a variety of personal risk factors. A recent review stated, "The original criterion of *specificity* is widely considered weak or irrelevant from an epidemiologic standpoint."¹⁰⁵ Asbestos, for example, is associated with a range of cancers and various exposures. Regardless of doubts about the meaningfulness of this factor, talcum powder products are primarily associated with ovarian cancer and thus fulfills the specificity consideration, although this consideration is not one of the most important considerations for causality in my expert opinion.

D) Temporality

An exposure must come before an outcome for the exposure to be causal. Bradford Hill explained that for an exposure-disease relationship to be causal, exposure must precede the onset of disease. While this is self-evident, in epidemiological studies, reverse causality, in which behavior related to a health issue is influenced by knowledge or events about the issue, is always a concern. For example, women who undergo ovarian cancer treatment may begin using talcum powder products during their pre- and post-operative period because of symptoms or side effects perceived to be alleviated by talcum powder products use. Assessing talcum powder use without specifying the time of use might lead to women with ovarian cancer being more likely to report talcum powder products use. In this example, talcum powder may not have caused the cancer; rather, use of talcum powder products was caused by the cancer (and treatments). The importance of this issue led to Bradford Hill's consideration of temporality when assessing causality.

In essentially all of the case-control studies that assessed use of talcum powder products, women were specifically asked to report talc powder products only during past, not current periods; thus, the studies explicitly assessed exposure to talcum before cancer. Typically, questions were phrased "Did you ever use talc, but not in the last year before cancer diagnosis?" to exclude the year prior to diagnosis. This issue is not relevant for the included cohort studies, as women were surveyed about their exposures prior to cancer ascertainment. Thus, the temporality consideration is important for my consideration and is satisfied.

E) Dose Response

In general, when risks are proportional to exposure (e.g., doubling exposure doubles risk) this dose-response evidence is considered to support causality. Many of the reviewed studies did not collect sufficient data to carefully quantify the dose response, and many limited their comparisons to an ever/never comparison. This is in part what motivated me to complete my separate quantitative review to at least be able to dis-entangle ever into regular versus not regular use. The reviewed studies that did provide data that could be used to assess the

potential for dose response had mixed results in quantifying dose response. While most studies showed evidence of a dose response, others did not. For example, Schildkraut showed that >20 years of any genital powder use (OR 1.51, 95% CI 1.11, 2.06) showed a stronger association with ovarian cancer than <20 years of use (OR 1.33, 95% CI 0.95, 1.86).⁹⁹ Terry and Harlow showed significant dose responses, where ORs increased as exposures increased.^{69,74} The adjusted ORs increased from 1.3, to 1.5 to 1.8 with <1000, 1000–10,000, and >10,000 lifetime applications. Overall, any exposure to talcum powder resulted in an OR of 1.5; direct perineal application had an OR of 1.7 (95% CI 1.1, 2.7), daily exposure had an OR of 1.8 (95% CI 1.1, 3.0) and women with an intact genital tract who were estimated to have had more than 10,000 applications during ovulating years had the highest risk (OR 2.8 95% CI 1.4, 5.4). This exposure was found in 14% of women with ovarian cancer. Penninkilampi⁶⁷, the most comprehensive of the systematic reviews, also showed a dose response where women with more than 3600 lifetime applications had slightly higher risks as did women who reported long-term (>10 years) talc use. In contrast, Whittemore⁷⁷ showed no dose response, and Booth⁷⁸ demonstrated the reverse—the higher the dose, the lower the risks. The data from reviewed studies were too diverse to summarize a dose-response relationship. The measures of exposure frequency and duration varied, and the studies used different thresholds for quantifying exposures. Further, the measures to quantify dose tended to be crude, making the response even more difficult to establish.

In summary, most but not all studies of talcum powder products and ovarian cancer show a dose response, but the results are inconsistent, and more importantly, are not considered or assessed in most of the published studies. A dose-response relationship is not required for causality and in large part because data were not consistently available, this factor does not weight heavily in my consideration. Further, this factor did not weight heavily in my considerations in that not all exposures will have a dose response, and some will indeed have a threshold effect. This is important here because asbestos is believed to exhibit a threshold, rather than a linear, dose-response.

F) Biologic Plausibility: Factors Linking Talc and Ovarian Cancer

The epidemiological evidence suggests a strong and positive association between exposure to talcum powder products and invasive ovarian cancer. However, epidemiological evidence alone does not provide a mechanism or pathophysiological process that accounts for the increased risk. Nor does the epidemiological evidence confirm the specific component or ingredient in talc powder products that is responsible for carcinogenesis. Nonetheless, the data are persuasive that particles contained in talcum powder reach the tubes and ovaries, inflammation initiate a causal pathway, and that several components of talc powder products including asbestos, asbestiform fibers in talc, and heavy metals can contribute to the carcinogenicity of the products. This was a strong factor in my consideration of the evidence because there is extremely strong evidence that the components of talc powder products are known to be highly carcinogenic in other settings.

G) Coherence and Consistency with Understood Biology

The guideline of coherence is considered similar to biological plausibility. For both, the cause-and-effect explanation should be consistent with all knowledge available. For talcum powder and ovarian cancer, this consideration is easily satisfied.

H) Experimental Evidence

The evidence in humans of the impact of talcum powder products exposure and ovarian cancer development is based on a large number of observational studies. Direct experimental evidence in the form of randomized controlled trials in humans is simply not possible to generate, for ethical reasons. The experimental evidence in humans that talc particles can migrate to the ovary and be incorporated into ovarian tissue is relevant to developing a causal model but does not directly prove that that exposure causes cancer. There is also human data relating to the inflammatory nature of ovarian cancer. There is compelling in vitro research delineating the inflammatory mechanism by which talcum powder causes cancer. Animal studies showing inflammatory tissue effects and tumor formation with talcum powder exposure are also supportive.

I) Analogy

Bradford Hill implied that when evidence is strong of a causal relationship between a risk factor and disease, researchers should be more accepting of weaker evidence that a similar risk factor may cause a similar disease. Thus, analogy has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar. The strong evidence for the association between asbestos and lung cancer, and the chemical similarity between these minerals, as well as their fibrous nature, supports the analogy consideration and causal inference.

Summary: Consideration of Causality of Talc Powder Products and Ovarian Cancer using Bradford Hill

In consideration of Bradford Hill, the clear strength of the association (A), remarkable consistency in the published literature across a large number of populations and research studies (B), temporality (D) considered in all of the published studies, and perhaps most importantly, biological plausibility (F) were the criteria that I considered of paramount importance when assessing the causality of exposures of talc powder products and epithelial ovarian cancer

IX. Conclusion

In conclusion, substantial evidence supports a strong, positive and causal association between ovarian cancer and genital exposure to talcum powder products. Regular exposure to talcum powder products causes ovarian cancer in some women. This opinion is based on my extensive review of the medical and scientific literature, my own independent meta-analysis of the data, and my experience and expertise in the areas of epidemiology and women's health, including ovarian cancer.

All opinions are made to a reasonable degree of medical and scientific certainty. I reserve the right to amend or supplement this report as new information becomes available.

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Exhibit A

CURRICULUM VITAE
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EDUCATION

1980 - 1985	Princeton University	BSE	Engineering / Architecture
1985 - 1986	Columbia University		Post Bacc Pre-Med
1987 - 1991	University of California, San Francisco	MD	Medicine
1991 - 1992	University of California, San Francisco	Intern	Pathology
1992 - 1996	University of California, San Francisco	Resident	Radiology
1996 - 1997	University of California, San Francisco	Clinical Instructor	Radiology, Ultrasound
1996 - 1998	University of California, San Francisco	Fellow	Epidemiology & Biostatistics

LICENSES, CERTIFICATION

1992	California Medical License # G76462
1993	California X-ray Supervisor and Operator License RHL 143658
1996	Board Certification, American Board of Radiology

PRINCIPAL POSITIONS HELD

1998 - 2003	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Assistant Professor
2003 - 2009	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Associate Professor
2009 - current	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Professor
2014 - current	UCSF, Phillip R. Lee Institute for Health Policy Studies	Member
2000 - current	UCSF, Radiology Outcomes Research Lab	Director

OTHER POSITIONS HELD CONCURRENTLY

1999 - 2000	St Bartholomew's and The Royal London School of Medicine	Research Fellow
2009 - 2010	NIH, National Cancer Institute, Radiation Epidemiology Branch	Research Scientist

HONORS AND AWARDS

1985	Cum laude, Princeton University
1985	Senior Thesis Prize, Princeton University
1991	Student Summer Research Fellowship, Institute for Health Policy Studies, UCSF
1999, 2000	Nycomed Amersham Fellow, Radiologic Society of North America
2007	Nomination, Clinical Research Mentor of the Year, Bay Area Symposium on Clinical Research
2010	Nomination, CTSI Consultant of the Year, Impact Award
2010	Scientific Paper of the Year, Minnies, Auntminnie.com
2010	Finalist, Most Influential Radiology Researcher, Minnies, Auntminnie.com
2011	Leader in Imaging, Auntminnie.com
2012	Finalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2012	Semifinalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2012	Winner, UCSF Center for Health Care Value, Medical Center Initiative, Innovation Award
2013	Finalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2013	Runner-up, Scientific Paper of the Year, Auntminnie.com, Minnies
2013	Paper honored as 1 of the top 10 publications Funded by NCI's Epidemiology and Genomics Research Program
2014	Invited Editor, J of the American College of Radiology, March 2014, Radiation Dose Optimization
2014	Among Philip R. Lee Institute for Health Policy Studies faculty videos on UCTV, "Is Medical Imaging Harmful to Health: Opportunities to Influence Health Policy", most popular, N = 409,937
2015	Academy of Radiology Research, Distinguished Investigator Award
2015	Election to Fellowship, Society of Radiologists in Ultrasound

KEYWORDS AND AREAS OF INTEREST

Health Services Research, Outcomes Research, Disparities Research, Women's Imaging, Comparative Effectiveness Research, Quality Improvement, Dissemination and Implementation Sciences, Evidenced Based Radiology, Assessment of Population Impact of Screening Tests, Radiation Associated with Medical Imaging, Radiation as an Environmental Cause of Cancer, Management of Incidental Findings on Diagnostic Testing

OVERVIEW

Narrative

Dr. Smith-Bindman is a clinical researcher with expertise in health services research, epidemiology, outcomes research, comparative effectiveness research, and dissemination and implementation sciences focused on diagnostic imaging. Her research has focused on evaluating the quality, utilization, accuracy, predictive values and impact of diagnostic testing on patient health, and has quantified both the risks and benefits of medical imaging when used in different contexts and by different populations. One area of focus has been on evaluating racial and ethnic differences in access and utilization of screening mammography and how that contributes to higher breast cancer mortality among African American women, and on factors that influence the quality and access to screening among vulnerable populations (see references 33, 34, 37, 43, 46, 48, 61, 67 at the end of CV). A separate area of focus has been on quantified the variation in radiation dose associated with medical imaging across patients and institutions, and quantified the impact of radiation, particularly from computed tomography, as an environmental carcinogen. (see references 53, 58, 60, 62, 65, 68, 69, 72, 76, 78, 79., 81, 87, 89, 91, 97, 102, 107.) Separate from her research activities, she has been actively involved in translating evidence into changes in practice and policy. She has *informed policy leaders, practitioners and the public about* the safety concerns surrounding the use of radiation in imaging by describing the issue in main stream media, testifying before the US Congress, and by advising the FDA, The Joint Commission, the International Atomic Energy Agency, the International Council on Radiation Protection and leading professional societies. She has also written quality measures focused on radiation safety, and her work has resulted in organizations which monitor health care quality to adopt measures of diagnostic imaging safety.

Significant Publications

1. **Smith-Bindman** et al. Ultrasound vs Computed Tomography for Suspected Nephrolithiasis NEJM. 2014; 371:1100-10
2. Miglioretti DL, Johnson E, William SA, Grenlee RT, Weinmann S, Solberg LI, Feigelson HS, Roblin D, Flynn MJ, Vanneman N, **Smith-Bindman R**. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013 167 (88): 700-7
3. **Smith-Bindman R**, et al. Risk of Thyroid Cancer based on Thyroid Ultrasound Imaging Characteristic: Result of A Population Based-Study. JAMA Internal Medicine. 2013 173(19):1788-96
4. **Smith-Bindman R**. Appendix F. Ionizing Radiation Exposure to the US Population, with a Focus on Radiation from Medical Imaging, included in Breast and the Environment: A Life Course Approach. The Institute of Medicine. March 20 2012
5. **Smith-Bindman R et al**. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. JAMA Internal Medicine 2009;169(22):2078-86
6. Curtis E, Quale C, Haggstrom D, **Smith-Bindman R**. Racial and Ethnic Differences in Breast Cancer Survival: How Much Is Explained By Screening, Tumor Severity, Biology, Treatment, and Co-morbidities. Cancer 2008 112(1):171
7. Goldman L, Haneuse S, Miglioretti D, Kerlikoswke K, Buist D, Yankaskas B, **Smith-Bindman R**, An assessment of the quality of mammography care at facilities treating medically vulnerable populations Medical Care 2008 46(7):701-8.
8. **Smith-Bindman et al**. Does Utilization of Screening Mammography Explain Racial and Ethnic Differences in Breast Cancer? Ann Intern Med. 2006; 144(8):541-53
9. Haggstrom DA, Quale C, **Smith-Bindman R**. Differences in the Quality of Breast Cancer Care Among Vulnerable Populations. Cancer. 2005 Dec 1;104(11):2347-58.
10. **Smith-Bindman, R**, et al Endovaginal ultrasound to evaluate endometrial abnormalities. JAMA 1999;281:1693-4

PROFESSIONAL ACTIVITIES

CLINICAL

Attending physician, Ultrasound Section, Department of Radiology and Biomedical Imaging, UCSF, 25%. Includes supervised instruction of residents and fellows. My teaching focuses on how to use evidence to help inform interpretation of clinical examinations.

PROFESSIONAL ORGANIZATIONS

Memberships

1997 - 2018	Society of Radiologists in Ultrasound (SRU)
1997 - 2018	Radiology Alliance for Health Services Research in Radiology (RAHSR)
2013 - 2018	American College of Radiology (ACR)
2014 - 2018	American Roentgen Ray Society (ARRS)
2014 - 2018	Association of University Radiologists (AUR)

Service to Professional Organizations (selected)

2010 - 2011	American Board of Medical Specialties, American Board of Radiology, American College of Radiology, and Physician Consortium for Performance Improvements. Patient Radiation Dose Work Group
2011 - 2012	Institute of Medicine Committee on Breast Cancer and the Environment, commissioned report "Temporal Changes in Ionizing Radiation and Estimate of Contributions to Breast Cancer," contributing author
2012	Centers for Disease Control and Prevention, Cancer Prevention Work Group
2012 - 2014	The Joint Commission, Diagnostic Ionizing Radiation and Magnetic Resonance work group focused on issues of safety and guideline development
2012 - Present	International Council on Radiation Protection (ICRP) Task Group #79 on Defining Effective Dose Use in Medicine
2014	International Atomic Energy Agency (IAEA) United Nations General Assembly and Security Council. Special Committee Considering Population Impact of Low Dose Radiation
2015	Council of Distinguished Investigators of the Academy of Radiology Research

Service to Professional Publications (selected)

2000 - 2018	Journal of the American Medical Association (JAMA)
2000 - 2018	JAMA Internal Medicine
2000 - 2018	New England Journal of Medicine (NEJM)
2000 - 2018	Radiology
2000 - 2018	American Journal of Radiology
2000 - 2011	Journal of the National Cancer Institute
2000 - 2011	Health Affairs

2000 - 2015	Health Services Research
2000 - 2010	American Journal of Obstetrics & Gynecology
2000 - 2010	American Journal of Public Health
2000 - 2010	Annals of Internal Medicine
2000 - 2010	Journal of Medical Screening
2000 - 2010	Journal of Women's Health
2000 - 2010	Medical Care
2000 - 2010	Medical Decision Making
2000 - 2010	Obstetrics and Gynecology
2000 - 2010	Ultrasound in Obstetrics & Gynecology

INVITED PRESENTATIONS

International

2001	US - UK Cancer Learning Network, Deprivation and Cancer, <i>London, United Kingdom</i>
2001	British Society of Human Genetics, Prenatal Screening for Down syndrome in England and Wales and Birth Outcomes, <i>London, United Kingdom</i>
2002	Global Summit on Mammographic Screening, Europe Institute of Oncology, U.S.-U.K. Comparison of Screening Mammography, <i>Milan, Italy</i>
2005	University of Copenhagen, Does Practice Make Perfect; Association Between Volume and Accuracy of Mammography, <i>Copenhagen, Denmark</i>
2006	International Society for Prenatal Diagnosis, Prenatal Screening for Down syndrome in The Second Trimester of Pregnancy, <i>Kyoto, Japan</i>
2009	Canadian Breast Cancer Foundation, Forum on the Earlier Detection and Diagnosis of Breast Cancer, <i>Toronto, Canada</i>
2010	Nation Cancer Research Institute (NCRI), Risk of Cancer from Computed Tomography Examinations, <i>Liverpool, United Kingdom</i>
2013	Bach Mai University Hospital, Radiation for Medical Imaging: A Hidden Epidemic, <i>Hanoi, Vietnam</i>
2014	International Atomic Energy Agency (IAEA), Health Effects of Exposure to Low Dose Ionizing Radiation Associated with Medical Imaging, <i>Vienna, Austria</i>
2014	Korea College of Radiology, Tracking and Monitoring Radiation Dose and Its Impact Across the University of California Medical Centers and CT Radiation Doses Are Not What You Think: Why It's Important to Monitor and Track Dose Seoul, Republic of Korea
2016	International Atomic Energy Agency (IAEA), Exposure to low dose ionizing radiation from medical imaging and the health effects from these exposures. International Atomic Energy Agency. Technical Meeting on Science, Technology and Society Perspectives on Nuclear Science, Radiation and Human Health: The View from Asia, Singapore University
2016	University of North Carolina School of Medicine, Chapill Hill, NC, Radiology Department Grand Rounds , Diagnostic Imaging: Increasing Effectiveness and Safety Radiation From Medical Imaging,

- 2016 Singapore General Hospital, Singapore. Radiology Grand Rounds. Visualizing Patients and Their Dose to Improve Health Care Quality,
- 2016 St Luke's International Hospital, Tokyo, Japan. Hospital-wide grand rounds, Radiation from Medical imaging: A Hidden Epidemic.
- 2017 Childhood Leukemia International Consortium, Annual Meeting, Minneapolis, Minnesota, Estimating Radiation Exposure from Imaging Procedures
- 2017 Charity Hospital, Berlin, Germany. Radiology Grand Rounds, Radiation from Medical Imaging: A Hidden Epidemic
- 2017 Charity Hospital, Berlin, Germany, Imaging for Suspected Nephrolithiasis: Results from the Randomized Controlled Trial
- 2017 University Hospital, Basel, Switzerland, Radiology Grand Rounds. A Dose of Reality: The Need for Active CT Dose Management
- 2017 Center for Diagnostic Imaging Quality Institute Council of Medical Directors, Scottsdale, AZ Keynote: Radiation from Medical Imaging
- 2017 The Leap Frog Group Pediatric Computed Tomography Radiation Dose
- 2017 PCORI Advisory Panel on Communication and Dissemination Research Presentation UCSF CT Radiation Dose Registry to Ensure a Patient-Centered Approach for Imaging
- 2017 American Urological Association (AUA) Quality Improvement Summit, Baltimore Maryland Keynote Address. Imaging Wisely: Improving the Value of Medical Imaging
- 2018 Jakarta Radiology Society, Jakarta Indonesia. Dose Optimization Implementation to achieve better radiology service in Hospital Keynote Addresses: Radiation from Medical Imaging: A Hidden Epidemic and Optimizing Radiation Doses for CT
- 2018 Westmead Hospital Sydney Australia. Radiology Grand Rounds. Radiation from Medical Imaging: A Hidden Epidemic
- 2018 Westmead Childrens Hospital, Sydney Australia. Optiizing Radiation Doses For Pediatric CT
- National
- 2000 American College of Medical Genetics
- 2000 Society of Radiologists in Ultrasound
- 2000 Society for Health Services Research in Radiology
- 2001 Society of Radiologists in Ultrasound Annual Meeting

2001	Society for Health Services Research in Radiology
2002	Society of Radiologists in Ultrasound
2003	Breast Cancer Surveillance Consortium
2003	Society of Radiologists in Ultrasound
2003	Centers for Disease Control and Prevention
2003	RSNA 88th Scientific Assembly and Annual Meeting
2004	Institute of Medicine (IOM): Saving Women's Lives
2004	Breast Cancer Surveillance Consortium
2005	Improving Mammographic Quality Standards Institute of Medicine (IOM)
2006	Beth Israel Deaconess Medical Center, Grand Rounds
2006	National Institute Child Health and Human Development
2007	National Cancer Institute, National Institute of Health (x2)
2008	Mount Sinai Urban Health Institute; Metro Chicago Breast Cancer Taskforce, Partnerships in Translation: Advancing Research and Clinical Care
2008	University of Washington, Seattle, Washington, Grand Rounds, and Visiting Professor,
2008	HMO Research Network Conference (4 th annual), Danville, Pennsylvania
2009	Society of Radiologists in Ultrasound, National Conference on Management of Ovarian Cysts
2009	Canadian Forum for the Earlier Detection and Diagnosis of Breast Cancer
2010	Center for Disease Control & Prevention, Annual Cancer Registry Meeting, Atlanta, Georgia
2010	HMO Research Network conference, Emerging Frontier in Healthcare, Research Delivery, Austin, Texas
2010	National Council on Radiation Protection (NCRP), Communication of Radiation Benefits and Risks in Decision Making
2010	National Cancer Institute, Board of Scientific Advisors, Bethesda, Maryland
2010	American Statistical Association Conference on Radiation Health, Annapolis, Maryland
2010	Breast Cancer Surveillance Consortium Annual Meeting, Washington, D.C.
2010	Kaiser Permanente: National Radiology Leadership Group, held at the RSNA, Chicago, IL
2011	Cleveland Clinic, Health Care Quality Innovation, Cleveland, Ohio
2011	Auntminnie.com, Live WebEx Conference RADEXPO 2011
2011	University of New Mexico, Visiting Professor, External Reviewer, Resident Research Day
2011	Oregon Health Sciences University, Department of Emergency Medicine, Grand Rounds
2012	Society for Imaging Informatics for Medicine (SIIM), San Francisco, CA
2012	Brown University, Grand Rounds, Emergency Medicine, RI Hospital, Providence, RI
2012	Society for Imaging Informatics in Medicine (SIIM), Los Angeles, CA

2012 PharmMed OUT, Georgetown University, Washington, DC

2012 Agency for Healthcare Research and Quality, Rockville, MD

2012 Radiology Society of North America, expert witness in full day mock trial focused on radiation safety and whether radiologists need to communicate risks to patients, Chicago, IL

2012 University of Pennsylvania, Grand Rounds, Emergency Medicine, Philadelphia, PA

2013 Radiology Society of North America (RSNA), Controversies Session, CT Radiation and Risk: How Certain Are We of the Uncertainty? Chicago, IL

2013 American Cancer Society, Doc Talk Lecture Series

2013 Association of University Radiologists (AUR), Comparative Effectiveness and Patient-centered Outcomes Research, Los Angeles, CA

2014 Cancer.net Podcast, "CT Scans and Cancer Risk", Available Online at <http://www.cancer.net/blog/2014-10/ct-scans-and-cancer-risk>

2014 Oregon Chapter, American College of Emergency Physicians, Portland, Oregon

2015 Women in Government Foundation (non-profit, non-partisan organization of all U.S. female state legislators) Diagnostic Imaging. Increasing Its Effectiveness and Safety, at 16th Annual Southern & Eastern Regional Conference, Charleston S Carolina

2016 Lindeberger Cancer Center, University of North Carolina, Chappil Hill NC, Radiation From Medical Imaging: A Hidden Epidemic

2017 American Urological Association (AUA) Quality Improvement Summit, Baltimore Maryland Keynote Address. Imaging Wisely: Improving the Value of Medical Imaging

Regional Presentations (selected)

2000 Kaiser Permanente Department of Genetics, Oakland CA

2001 San Francisco State University, SF CA

2001 UCSF, San Francisco General Hospital, Department of Medicine, Grand Rounds

2001 American College of Obstetrics and Gynecology

2002 UCSF Breast Oncology Program Comprehensive Cancer Center Grand Rounds

2003 UCSF Obstetrics and Gynecology Grand Rounds, SF CA

2004 UCSF Multi-Department Symposium. Racial Disparity and Breast Cancer, SF CA

2004 UCSF Quality of Breast Cancer Care Symposium, SF CA

2005 Sisters Network, San Francisco (African American Advocacy Organization)

2005 Stanford University, Department of Health Research and Policy, Grand Rounds, Palo Alto CA

2006 UCSF, Lunch and Learn: San Francisco Community Outreach, SF CA

2006 Bay Area Health Care and Quality Outcomes, San Francisco, CA

2007 California Breast Cancer Research Symposium, Los Angeles, CA

2010 Bay Area Clinical Research Symposium, Plenary Speaker, San Francisco CA

2011	UCSF Department of Medicine Grand Rounds, San Francisco, CA
2011	San Francisco General Hospital Department of Medicine, Grand Rounds, San Francisco, CA
2011	UCSF, Department of Urology Grand Rounds, San Francisco, CA
2011	UCSF Department of Radiology Grand Rounds, San Francisco, CA
2011	Eden Hospital, Department of Medicine Grand Rounds, Alameda, CA
2011	Stanford Hospital, Department of Medicine, Grand Rounds, Palo Alto, CA
2011	Kaiser Permanente Medical Center, Multi-departmental Grand Rounds, San Francisco, CA
2011	UCSF Institute for Health Policy Studies, San Francisco, CA.
2012	Kaiser Permanente Medical Center, Grand Rounds, San Francisco, CA
2012	Kaiser Permanente Medical Center, Grand Rounds, Oakland, CA
2012	Massachusetts General Hospital, Department of Emergency Medicine, Grand Rounds Boston,
2012	Beth Israel Hospital, Department of Emergency Medicine Grand Rounds, Boston, MA
2012	Univ. of California Office of the President, Quality Improvement and Technology, Oakland, CA
2012	UCSF, Department of Radiation Oncology, Grand Rounds,
2012	Southern California Kaiser Radiology Chiefs Grand Rounds,
2014	UCSF, Endocrine Grand Rounds, San Francisco, CA
2015	California Society of Radiology Technologists, Annual Meeting, San Francisco, CA Keynote Address. Radiation from CT: A Hidden Epidemic. Strategies to minimize doses: What technologists can do?
2016	Society of Radiology in Ultrasound, Annual Meeting, Baltimore Maryland. Risk of Thyroid Cancer Based on Thyroid Ultrasound Imaging Characteristics
2016	UCSF, Breast Oncology Program, Radiation from Medical Imaging: A Hidden Epidemic and Approaches for Improving.
2016	UCSF Mini-Medical School Radiation Safety and Medical Imaging
2017	University of California Davis, Radiology Grand Rounds, Radiation from Medical Imaging; A Hidden Epidemic
2017	UCSF: Stand Up for Science: Panel Discussant

GOVERNMENT AND OTHER PROFESSIONAL SERVICE (selected)

2002 - 2003	CDC, National Breast and Cervical Cancer Early Detection Program, Planning Committee
2002 - 2005	Cochrane Collaboration Screening and Diagnostic Tests, Methods Working Group
2003 - 2003	Radiology National Boards, Examination Question Writer
2003 - 2010	National Cancer Institute, Physician Data Query (PDQ)

2004 - 2005	CDC, National Breast and Cervical Cancer Early Detection Program, Panelist, Committee on Assessment of Covered Benefits, Expert
2007 - 2010	California Health Benefits Review Program (CHBRP)
2008 - 2011	Center for Scientific Review, NIH, Health Services Organization and Delivery Study Section
2010 - 2011	American Board of Medical Specialties, American Board of Radiology, American College of Radiology, and Physician Consortium for Performance Improvements. Patient Radiation Dose Work Group
2010	Congressional Hearing, US House of Representatives, Energy and Commerce, Subcommittee on Health. Medical Radiation: An Overview of the Issues. Expert Witness
2010	Food and Drug Administration, Center for Devices & Radiological Health, National Meeting Focus on Radiation Safety, Presenter
2010 - 2011	National Quality Forum, Imaging Efficiently Steering Committee
2011 - 2012	Institute of Medicine Committee on Breast Cancer and the Environment, commissioned report "Temporal Changes in Ionizing Radiation and Estimate of Contributions to Breast Cancer," contributing author
2010 - 2011	Lung Cancer Screening with CT Evidence Review Committee. Multidisciplinary collaboration, including American Cancer Society, American College of Chest Physicians; American Society of Clinical Oncology & The National Comprehensive Cancer Network
2011 - 2016	International Council on Radiation Protection (ICRP), Task Group 79 on Defining Effective Dose Use in Medicine
2012	Congressional Hearing, US House of Representatives, Energy and Commerce, Subcommittee on Health, hearing on the Consistency, Accuracy, Responsibility, and Excellence in Medical Imaging and Radiation Therapy (The CARE Bill), Expert Witness
2012	Centers for Disease Control and Prevention, Cancer Prevention Work Group
2012 - 2014	The Joint Commission, Diagnostic Ionizing Radiation and Magnetic Resonance work group focused on issues of safety and guideline development
2013	Government Accountability Office: Medicare Imaging Accreditation Establishing Minimum National Standards and an Oversight Framework to Ensure Quality and Safety of Advanced Diagnostic Imaging Services, May 2013, Contributor
2014	International Atomic Energy Agency (IAEA) United Nations General Assembly and Security Council. Special Committee Considering Impact of Low Dose Radiation
2015	Council of Distinguished Investigators of the Academy of Radiology Research

UNIVERSITY AND PUBLIC SERVICE

Service Narrative

There are several activities to which Dr. Smith-Bindman has contributed. For seven years she participated in the NCI sponsored Physicians Data Query (PDQ), an NCI committee charged with presenting evidenced based, on-line, widely accessible and widely disseminated guidelines relating to cancer screening and diagnosis. She

participated in several activities related to breast cancer screening including acting as a reviewer for the CDC on assessing the guidelines for the National Breast and Cervical Cancer Detection Program, participating in coverage decisions, acting as reviewer and content expert for the CA Health Benefits Review Program analyzing several bills before the state legislature that would expand breast cancer screening to include MRI, and participating in the creation of several IOM Reports. She has participated in several community projects, such as acting on the board of an African American breast cancer advocacy group, and as a consultant to the Metropolitan Breast Cancer Task Force, charged with improving breast cancer mortality rates and racial disparities. During the last five years She has been very active in local, statewide and national efforts around improving radiation safety, including invited presentations to the FDA, testifying before the US Congress on two occasions, working with innumerable societies and government organizations on guidelines and submitting two endorsed quality measures on radiation safety to the National Quality Forum. Her involvement in service activities within the University have focused on increasing the quality and quantity of translational research through participation in several University-wide task forces. Dr. Smith-Bindman serves on several Medical Center Committees, focusing on improved oversight and stewardship around radiation, and projects to improve the efficiency and effectiveness with CT.

UNIVERSITY SERVICE (selected)

2001 - 2015	UCSF School of Medicine, Faculty Recruitment Committees, Radiology, Rad Onc, Medicine
2002	UCSF School of Medicine Dean's Leadership Retreat, Santa Cruz
2003	University of California, Blueprint for Regional Excellence in Breast Cancer Care
2003	UCSF School of Medicine Task Force, Future of UCSF and Mission Bay
2003	UCSF Medical Center, Hospital Exceptional Physician Award, Committee Co-Chair
2003 - 2004	UCSF School of Medicine Task Force, Physician Scientist Program Clinic-Based
2003 - 2005	UCSF School of Medicine Faculty Council
2005	UCSF School of Medicine, Dean's Leadership Retreat, Santa Cruz, CA
2005 - 2006	UCSF Department of Radiology Seminars and Presentation Committee
2005 - 2008	UCSF Department of Radiology Annual Research Symposium Abstract Review Committee
2005 - 2009	UCSF Department of Radiology, SEED Grant Review Committee
2006 - 2007	UCSF Pathways for Clinical and Translational Research
2008 - 2010	UCSF Pathways to Discovery, Clinical and Translational Research, Advisory Council
2007 - 2010	University of California, Office of the President, CA Health Benefits Review Program
2009 - 2017	UCSF, Radiation Safety Committee
2012 - 2014	UCSF Department of Radiology, Maintenance of Certification Committee
2012 - 2015	UCSF Medical Center, Center for Health Care Value
2013 - 2017	UCSF School of Medicine, Conflict of Interest Advisory Committee
2014 - 2016	UCSF Clinical Enterprise, Strategic Plan, Committee for Continuous Process Improvement
2015 - 2017	UCSF Clinical Enterprise, Utilization Management Committee

PUBLIC SERVICE

2003 – 2007	SF Sisters, an African American breast cancer advocacy group, board member
2008 - 2008	Metropolitan Chicago Breast Cancer Task Force, Chicago IL, unpaid consultant
2011 - 2014	National Quality Form, National Consensus Standard for Patient Safety. Measure Developer "UCSF CT Radiation Dose Patient Safety Measure" Measure endorsed
2015	National Quality Forum, Pediatric Measures. Measure Developer, "Pediatric Computed Tomography Radiation Dose" Measure endorsed

TEACHING AND MENTORING

Teaching Narrative

Dr. Smith-Bindman spends substantial time mentoring trainees in clinical research. The trainees have ranged in experience from high school students through mid-career UCSF faculty. The individuals have come from a broad range of departments at UCSF including Radiology, Internal Medicine, Hospital Medicine, Emergency Medicine, Obstetrics and Gynecology, and Urology, and have also come from the UCSF Medical School, The University of California Berkeley, and local SF high schools. On average, she meets with each trainee 1-2 hours per week while collaborating. An NIH Mid-Career Investigator Award (K24) supported her time mentoring these individuals.

She teaches in several formal classes in the department of Epidemiology and Biostatistics primarily targeted to post graduate students who are completing a master's degree in clinical research. She is actively engaged in teaching the Radiology residents and fellows while attending on the clinical service and provides frequent lectures to the Radiology residents focused at research methods; frequently teaches in courses organized by the UCSF Office of Continuing Medical Education for both radiology courses and courses within other medical specialties. The radiology courses focus on using evidence to interpret our studies (usually focused on ultrasound topics), the lectures for other medical specialties focused on how to use imaging more appropriately. As listed above, she also frequently gives grand rounds within UCSF, and nationally on using imaging more appropriately. Lastly, she organized and ran a large, ongoing, virtual symposium on Radiation Safety described below. Both the content and format of this meeting were novel.

TEACHING

Formal scheduled classes for UCSF students.

The first class listed is a course for UCSF Medical Students. The remaining are part of the coursework offered within the UCSF Masters in Clinical Research Program, Department of Epidemiology and Biostatistics

Year	Title	Role	Class Size
2002 - 2005	Epidemiology and Biostatistics, UCSF School of Med	Section Leader	20
2005	Introduction to Diagnostic Testing	Lecturer	18
2007 - 2008	Clinical Performance and Health Outcome Measurement	Lecturer	20
2011 - 2014	Translating Evidence into Policy: Theory and Design	Lecturer	30
2010 - 2015	Framing Research to Influence Policy	Lecturer	25

Post Graduate CME courses (1-5 lectures/meeting)

2001	UCSF Obstetrics and Gynecology Update, San Francisco, CA
2001	UCSF Primary Care Medicine, Aspen, CO
2001	Primary Care Medicine, Maui, HI
2001	Management of the Hospitalized Patient, San Francisco, CA
2001	Controversies in Women's Health, San Francisco, CA
2001	Diagnostic Imaging in Women's Health, San Francisco, CA
2001	MRI & Ultrasound Imaging, Lake Tahoe, CA
2002	Obstetrics and Gynecology Update, San Francisco, CA.
2002	17th Annual Primary Care Medicine: Concepts and Controversies, Aspen, CO
2002	10th Annual Controversies in Women's Health, San Francisco, CA
2002	Diagnostic Imaging in Women's Health, San Francisco, CA
2002	Diagnostic Imaging, Maui, HI
2002	Obstetrical, Gynecological and Abdominal Ultrasound, San Francisco, CA
2003	Primary Care Medicine, Diagnostic Imaging in Women's Health, Maui, HI
2003	11th Annual Controversies in Women's Health, San Francisco, CA
2003	Diagnostic Imaging for Disease Prevention, San Francisco, CA
2003	46th Annual Diagnostic Radiology Postgraduate Course, San Francisco, CA
2003	OB/GYN and Abdominal Ultrasound, San Francisco, CA
2003	MRI and Ultrasound by the Lake, Lake Tahoe, CA
2004	Women's Imaging, Sonoma, CA
2004	Primary Care Medicine, Maui, HI
2004	Diagnostic Imaging in Clinical Practice, San Francisco, CA
2005	Obstetrical and Gynecologic Sonography, San Francisco, CA
2005	Radiology Spring Training, Scottsdale, Arizona
2005	Abdominal Imaging, Montreal and Quebec, Canada
2006	Controversies in Women's Health, San Francisco, CA
2006	Controversies in Breast Cancer Screening and Diagnosis, San Francisco, CA
2006	Cutting Edge Radiology, Diagnosis and Intervention, Vancouver, Canada
2008	Primary Care Medicine: Update 2008, San Francisco, CA
2008	Diagnostic Imaging in Women's Health, San Francisco, CA
2008	Obstetrical/Gynecological and Abdominal Sonography, San Francisco, CA
2009	Primary Care Medicine: Update 2008, San Francisco, CA

2009	Obstetrical/Gynecological and Abdominal Sonography Update, San Francisco, CA
2011	Imaging of Kidney Stones, San Francisco, CA, Director
2011	Primary Care Medicine, Principles & Practice, San Francisco, CA, Keynote
2011	39th Annual Advances in Internal Department of Medicine, San Francisco, CA, Keynote
2011	Controversies in Women's Health, Department of Medicine, San Francisco, CA, Keynote
2012	Updates on Imaging, Maui, Hawaii
2013	UCSF Otolaryngology Annual Conference, San Francisco, CA
2017	UCSF Practical Body Imaging, Kona, Hawaii

Other Teaching

Radiation Safety and CT: Virtual Symposium. Innovative on-line Interactive CME course targeted to physicians (radiologists and those who order imaging), technologists, medical physicists, and trainees. This was created as an on-line, free, virtual meeting focuses on radiation safety. The initial creation of this virtual meeting began in 2013. Creating the meeting involved creating a multidisciplinary, on line, virtual meeting with over 100 lectures (see list of lectures, now offered freely on line - <http://rorl.ucsf.edu/speakers>), 10 live interactive sessions/chat rooms and over 500 registrants enrolled in the meeting during the “live days”, and ongoing attendees attend each month. The speakers at the meeting included numerous department chairs, the director of the Agency for Health Care Policy at the time, a US Congressman, leaders from numerous societies, The Joint Commission, The American Board of Internal Medicine Foundation, and innumerable scientific experts on diverse patient safety issues, and the meeting was an integration of diverse viewpoints and perspectives. Dr. Smith-Bindman directed this meeting and personally wrote and delivered 7 lectures for the meeting. The meeting was novel in format and content.

MENTORING

Pre-doctoral students directly supervised

Dates	Name	Program or School	Current Position
2004 - 2005	C. Kagay	UCSF Medical School	Radiologist, Private Practice
2005 - 2006	A. Ding	UCB/ UCSF MD/MPH	MGH
2005 - 2008	A. Venkatesan	UCSF Medical School	Resident, Stanford
2006 - 2007	E. Dinkelspiel	Urban High School	Student, Univ. of Chicago
2011 - 2015	J. Keegan	Lick Wilmerding High	San Luis Obispo College
2010 - 2015	P. Mehta	UC Berkeley/UCLA Med School	UCLA Medical School
2012 - 2013	J. Zhang	UC Berkeley	Senior
2014 summer	A. Fraser	University High	Georgetown College

Postdoctoral fellows and residents directly supervised

Dates	Name	Position	Current Position
1998 - 2000	M. Copanigro, MD	Radiology Resident / Fellow	Private Practice

1998 - 2000	N. Vincoff, MD	Radiology Resident / Fellow	Private Practice
2003 - 2004	E. Weiss, MD	OB GYN Resident	Private Practice
2003 - 2005	K. Schueler, MD	RORL Research Fellow	Private Practice
2003 - 2005	D. Haggstrom, MD	Internal Medicine Fellow	Indiana University, Faculty
2005 - 2006	K. Reid, MD	Internal Medicine Fellow	Emory Faculty
2005	A. Jensen	PhD student, Copenhagen	Faculty
2005 - 2006	B. Ching, MD	Radiology Fellow	Private Practice,
2005 - 2006	A. Cole, MD	Radiology Fellow	Private Practice
2005 - 2007	L. Goldman, MD	Internal Medicine Fellow	UCSF Faculty
2006 - 2010	J. Lipson, MD	Radiology T32 Scholar	Stanford Faculty
2007 - 2008	J Stengel, MD	Radiology Fellow	Private Practice
2007 - 2008	A. Heath, MD	RORL Research Fellow	Private Practice
2007 - 2009	R. Cho, MD	Radiology Fellow	Private Practice
2007 - 2009	D. Sellami, MD	Radiology Resident / Fellow	Private Practice
2008 - 2009	A. Kamath, MD	Radiology T32 Scholar	NYU Faculty
2009 - 2010	J Ching, MD	OB GYN Resident	Faculty
2009 - 2011	N, Brasic, MD	Radiology Fellow	UCSF Faculty
2010 - 2011	D. Sridhar, MD	Radiology Resident	Private Practice
2010 - 2012	P. Lebda, MD	Radiology Fellow	Cleveland Clinic Faculty
2010 - 2013	I. Burger, MD	Radiology Resident	Private Practice
2010 - 2013	G. Merry, MD	Radiology Resident	Private Practice
2011 - 2014	J. Mongan, MD PhD	Rad Resident / Fellow	UCSF, Faculty
2013 - 2014	S. Hou, MD	Radiology Resident	NYU Faculty
2013 - 2014	C. Lee, MD	Radiology Resident	UCSF Faculty
2013 - 2014	T. Morgan, MD	Radiology Resident	UCSF Faculty
2013 - 2015	LA Hampton, MD	Urology Resident / Fellow	Fellow, Wash U
2013 - 2015	V. Arasu, MD	Radiology Resident	Resident
2013 - 2015	N. Benedetti, MD	Radiology Resident	University of Wash Faculty
2014 - 2015	B Carpenter, MD	Radiology Fellow	UCSF Faculty
2014 - 2015	J. Hsu, MD	Radiology Fellow	Private Practice
2014 - 2018	J. Demb	Epidemiology	UCSF

Faculty Mentoring

Dates	Name	Department / Section	Current Position
2002 - 2005	John Shepherd, MD	Radiology / Musculoskeletal	UCSF, Faculty, Radiology
2004 - 2005	Elaina Curtis, MD	UCSF Visiting Fellow	Univer. of Auckland Faculty
2005 - 2006	John Stein, MD	Emergency Medicine	UCSF Faculty, Emerg Med
2005 - 2006	Max Wintermark, MD	Radiology / Neuro	UVA, Faculty, Radiology
2007 - 2013	Lauren Goldman, MD	Internal Medicine	UCSF, Faculty, Medicine
2008 - 2011	Larry Rand, MD	OBGYN / Maternal Medicine	UCSF, Faculty, OBGYN
2008 - 2014	Antonio Westphalen, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2009 - 2017	Liina Poder, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2010 - 2018	Ralph Wang, MD	Emergency Medicine	UCSF Faculty, Emerg Med
2014 - 2018	John Mongan, MD, PhD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2017	Cindy Lee, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2017	Tara Morgan, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2018	Maureen Kohi, MD	Radiology / Interventional	UCSF, Faculty, Radiology
2015 - 2018	Ben Franc, MD PhD	Radiology / Nuclear Medicine	UCSF, Faculty, Radiology
2017 - 2018	Brian Haas MD	Radiology	UCSF, Faculty, Radiology

RESEARCH AND CREATIVE ACTIVITIES

Research Narrative

Dr. Smith-Bindman's research focuses on understanding the impact of diagnostic testing on patient outcomes. She is the director of the UCSF Radiology Outcomes Research Laboratory, and her team includes several programmers, biostatisticians, a developer, and a handful of epidemiologists who serve as project managers for the funded grants below. Her research expertise is in areas of epidemiology, technology assessment, outcomes research, comparative effectiveness research, health services research, and dissemination and implementation sciences focused on imaging. The research has focused on evaluating the quality, utilization, accuracy, predictive values and impact of diagnostic testing on patient health, and has quantified both the risks and benefits of medical imaging when used in different contexts and by different populations. I am leading several studies that assess and standardize the radiation dose used for CT scanning, in order to minimize doses, without loss of diagnostic accuracy. Additional current research is focused on putting systems-based solutions in place to standardize the use of imaging. For example, ongoing projects focus on improving decision support provided to physicians to help improve the use of testing, using evidence to drive and guide the change in practice, and determining the optimal surveillance strategy for the follow up of incidental findings seen on CT imaging. The research projects she leads, listed below, are typically collaborative, involving researchers from diverse clinical areas and who offer diverse methodological expertise.

RESEARCH AWARDS

Current

PI	07/02/2014 - 06/30/2019
NIH	\$1,140,000 direct/yr1
CT DOSE Collaboration: Partnership for Dose	\$7,900,000 total

Collaboration across the US and Europe to standardize and optimize the doses used for CT. The study uses a novel randomized controlled trial design to compare simple feedback to a multicomponent intervention as strategies to optimize doses. There are approximately 125 hospitals participating in the trial.

PI	09/02/2013 - 08/31/2016
PCORI (Patient Centered Outcomes Research Institute)	\$492,163 direct/yr1
CT Radiation Dose Registry to Ensure a Patient Centered Approach for Imaging	\$2,069,365 total

Collaboration across the US and Europe to create benchmarks and standards for CT by pooling data from a large number of hospitals and outpatient facilities

PI	3/01/2015- 02/28/2020
NIH	\$1,834,410 direct/yr1
Risk of Cancer in Childhood Associated with Medical Imaging	\$10,600,000 total

Retrospective cohort across large integrated health care systems to assess imaging in pregnant women and children and to quantify the risk of childhood and adolescent cancer associated with these exposures.

PI (co-PI with Gould, Kaiser Foundation Research)	4/01/2015- 03/30/2020
PCORI	
Pragmatic Trial of More versus Less Intensive Strategies for Surveillance of Patients with Small Pulmonary Nodules	\$14,458,936 total

Prospective comparative effectiveness study across 15 health care systems to compare different strategies for the surveillance of lung nodules. The study is novel in that patients will be recruited with routine clinical care at imaging and the creation of systematic quality improvement strategies to ensure no loss to follow up.

Past

PI	10/01/2010 - 09/30/2013
AHRQ	\$4,830,368 direct/yr1
RCT of US versus CT for Patients with Suspected Renal Colic	\$9,210,000 total

15 Center randomized pragmatic comparative effectiveness trial comparing different strategies for imaging patients with suspected kidney stones. The study exceeded enrollment and follow up targets, and the primary results were published in the NEJM in 2014. Many additional analyses are ongoing using these data.

PI	09/01/2008 - 07/31/2015
NIH K24	\$172,000 direct/yr1
Mid-Career Development Award: Risk of Cancer Associated with Incidental Findings	\$868,632 total

PI	07/01/2011 - 07/01/2014
University of California Office of the President, CHQI	\$250,000 direct/yr1
Standardization and Optimization of CT Radiation Dose	\$750,000 total

Across the University of California Medical Centers.

Five-center observational study to collect radiation data across the five University of California campuses using automated techniques, analyze the sources of variation in dose, and conduct quality improvement initiatives to standardize practice

PI	09/30/2012 - 09/29/2014
CDC (Centers for Disease Control and Prevention)	\$250,000 direct/yr1
PEDS CT-DOSE: Pediatric CT Dose Optimization and Standardization Endeavor	\$500,000 total

Ten center observational study to collect radiation data and create benchmarks in children

Co-Investigator (PI Solberg, Health Partners)	07/01/2012 - 06/30/2014
PCORI (Patient Centered Outcomes Research Institute)	\$250,000 direct/yr1
Measuring Patient Outcome from High Tech Imaging Studies	\$500,000 total

Mixed methods study to understand imaging use, positive rates of imaging and patient perspectives on imaging, with respect to identifying patient centered outcomes important to patients.

PI	04/01/2009 - 03/31/2011
NIH / R21	\$317,000 total
Risk of Cancer with Incidental Findings Identified on US Imaging	

Retrospective cohort to understand cancer risks of incidental findings

PI	09/01/2008 - 08/31/2010
NIH / R21	\$317,000 total
Radiation Exposure from Imaging: are Doses in a Carcinogenic Range	

Retrospective cohort to understand use of medical imaging within integrated health care systems

PI	10/01/1999 - 07/01/2005
DOD	\$725,515 total
Outcomes of Screening Mammography in Elderly Women	

Medicare Data were analyzed to determine utilization of mammography and factors influencing survival

PI	09/01/1999 - 06/01/2005
NIH K07	\$635,687 total
Outcomes of Screening Mammography in Elderly Women	

NIH Career development award to study breast cancer screening among elderly women.

PI	07/01/2003 - 02/01/2007
California Breast Cancer Research Program	\$583,287 total
Racial Disparity in Breast Cancer Mortality	

Retrospective cohort to understand the causes for racial disparity in breast cancer outcomes

Co-Investigator (PI Kerlikowske UCSF) 04/01/2000 - 03/31/2005
NIH, U01 **\$3,100,000 total**
San Francisco Mammography Registry: A Research Resource

Dr. Smith-Bindman project lead on 1) Physician Predictors of Mammography Accuracy and 2) Validation of the Medicare Screening Algorithm

Co-Investigator (PI – McCune, UCSF) 09/30/2006 - 06/30/2011
NIH
Clinical and Translational Science Institute (CTSI)

The grant is to enhance training and infrastructure across UCSF. I participate in the Biomedical Informatics Program to educate trainees about imaging, epidemiology and study design

Co-Investigator (PI- Lu, UCSF) 04/01/2006 - 03/01/2009
NIH
Statistical Methods for Evaluation and Validation of Tests

Co-Investigator (PI Tlsty, UCSF)) 10/01/2005 - 09/30/2010
NIH
Biological Basis of Breast Density and Breast Cancer Risk

Co-Investigator (PI Esserman, UCSF) 05/01/2003 - 04/30/2007
Department of Defense/USAMRC **\$6,900,000 total**
Blueprint for Regional Excellence in Breast Cancer Care

PI 01/01/2002 - 12/01/2006
Women's Health Research Center, UCSF **\$70,000 total**
Down Syndrome Screening in the US

PI 04/01/2001 - 04/01/2003
Society of Radiologists in Ultrasound **\$40,000 total**
Prenatal Ultrasound for Detection of Birth Defects and Chromosome Abnormalities

PI 04/01/2001 - 04/01/2004
Society of Radiologists in Ultrasound **\$30,000 total**
Physician Variation in Ultrasound Accuracy

PI 07/01/2000 - 06/01/2001 **\$40,000 direct/yr**
Society of North America
U.S. U.K Comparison of The Accuracy of Screening Mammography

P
I 07/07/1999 - 06/01/2000 **\$35,000 direct**
Radiologic Society of North America
Prenatal diagnostic ultrasound for the detection of chromosomal Abnormalities

MOST SIGNIFICANT RESEARCH PUBLICATIONS

- 1) **Smith-Bindman et al. Endovaginal ultrasound to evaluate endometrial abnormalities JAMA 1999**
Vaginal bleeding affects 7% of post-menopausal women, and historically women have undergone an invasive endometrial biopsy to exclude a diagnosis of cancer. This meta-analytic review found that endovaginal ultrasound is an easily tolerated non-invasive test that is accurate for the diagnosis of cancer, so that most women can avoid the need for an endometrial biopsy if they have a normal ultrasound test result. These results have been integrated into clinical practice guidelines in the US, Scotland, England, Germany, and Hong Kong. The publication has been cited 427 times based on SCOPUS accessed in 2015.
- 2) **Smith-Bindman et al. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. JAMA. 2001.**
Prenatal ultrasound is widely used to screen for Down syndrome, but the impact on patients has not been well studied. This meta-analytic review suggests that the use of ultrasound for the detection of fetuses affected by Down syndrome may be associated with more harm than benefit, as it can lead to large numbers of unnecessary amniocenteses and subsequent fetal losses with little evidence of benefits. This article was accompanied by extensive media coverage (AP, Reuters, NY Times), and controversy, and prompted discussion regarding the role of ultrasound in prenatal diagnoses. The manuscript has been cited 217 times based on SCOPUS accessed in 2015.
- 3) **Smith-Bindman R et al. US-UK Comparison of Screening Mammography. JAMA 2003.**
Screening mammography is an imprecise test, and there are considerable differences between physicians and programs in the accuracy of screening. This international comparison of screening mammography described 5.5 million mammograms obtained between 1996 to 1999 within three large-scale mammography registries or screening programs. Recall rates and open surgical biopsy rates were twice as high in the U.S. as in the U.K., although cancer rates were nearly identical. There was extensive media coverage (AP, Reuters, NY Times, Wall Street Journal, National Public Radio). These results have been widely cited, and were included in the IOM Report, "Saving Women's Lives." The publication was cited 223 times based on SCOPUS accessed in 2015.
- 4) **Smith-Bindman et al. Physician Predictors of Mammographic Accuracy. J Natl Cancer Inst 2005.**
Beyond the issues raised about the collective quality of mammographic screening in the United States, even more pronounced concern is the glaring variation among U.S. physicians in the ability to accurately interpretation their patients' mammograms. Dr. Smith-Bindman studied the accuracy of mammographic screening among 208 U.S. physicians, who collectively interpreted 1.2 million mammograms, and she found extraordinary variation in the interpretive abilities of radiologists; the sensitivity spanned 29% to 97%, while the false positive rate (the percentage of women who did not have cancer, but who underwent additional diagnostic testing or biopsy at their physician's recommendation) ranged from 1 to 29%. The difference in accuracy was principally due to differences in their training, experience and dedication to screening mammography; in short, the more experienced mammographers - and those who read more than the minimum number of mammograms required by MQSA guidelines - did substantially better. These findings have already been integrated into the Institute of Medicine's report on Mammography Quality Standards, regarding Enhancement of Interpretative Performance. The manuscript was cited 82 times based on SCOPUS accessed in 2015.
- 5) **Smith-Bindman et al. Does Utilization of Screening Mammography Explain Racial and Ethnic Differences in Breast Cancer? Ann Intern Med, 2006**
Racial and ethnic minorities tend to have larger, more advanced stage breast cancers at diagnosis than white women, and African American women have significantly higher breast cancer mortality. It has not been clear, however, if this is due to inherent differences in biology or the utilization of screening mammography. This paper sought to disentangle whether biology or the use of screening was largely responsible for the known racial and ethnic differences in breast cancer. This study was

unique in that detailed cancer information was available from tumor registries that were linked with detailed information regarding mammography utilization. The results were striking. Most of the racial and ethnic differences in breast cancer features were reduced or eliminated after accounting for the frequency of mammography screening. The manuscript was cited 175 times on SCOPUS.

6) **Smith-Bindman et al. Second trimester prenatal ultrasound for the detection of pregnancies at increased risk of Down syndrome. Prenat Diagn 2007** *Prenatal ultrasound is widely used to screen for Down syndrome, but the impact on patients has not been well studied. Our meta-analytic review found that ultrasound was not useful and this prompted our large prospective study which evaluated ultrasound in a larger cohort, including nearly 20,000 women, in whom nearly 500 had fetuses affected by Down syndrome. This large study confirmed these preliminary results. The manuscript was cited 51 times on SCOPUS.*

7) **Smith-Bindman et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. JAMA Internal Medicine 2009** *This paper documented the variation in doses associated with routine CT. The widespread media attention that this paper received contributed to active policy discussion in this area. I was invited to present and discuss the results at the FDA, at a Congressional Hearing sponsored by the Health Subcommittee of the Committee on Energy and Commerce, and innumerable professional society meetings, and submitted (and had endorsed) a measure of quality around CT imaging by the National Quality Forum. The manuscript was cited 857 times based on SCOPUS accessed in 2015.*

8) **Smith-Bindman R, Appendix F. Ionizing Radiation Exposure to the US Population, with a Focus on Radiation from Medical Imaging, in Breast and the Environment: A Life Course Approach. The Institute of Medicine. 2012** *The IOM was commissioned to write a report on environmental causes of breast cancer. The Komen Foundation commissioned the report. I was asked to summarize what is known about the harmful effects of ionizing radiation on breast cancer risks. The IOM concluded that ionizing radiation is one of the largest, and the most preventable causes of breast cancer.*

9) **Miglioretti DL et al. Smith-Bindman senior author. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013** *Using a retrospective cohort design, this paper quantified the use of imaging among children within one of 7 large integrated health care systems, quantified the radiation exposure associated with these examinations, and estimated the likely impact of improved standardization of the conduct of CT on the risks of cancer. The manuscript concluded that if the top outlying radiation exposures could be reduced to the average (a modest goal) that 40% of expected cancer could be eliminated. The manuscript was cited 150 times based on SCOPUS accessed in 2015*

10) **Smith-Bindman R, et al. Risk of Thyroid Cancer based on Thyroid Ultrasound Imaging Characteristic: Result of A Population Based-Study. JAMA Internal Medicine. 2013.** *This retrospective observational study documented the risk of cancer associated with specific thyroid imaging findings. This is the first study that links a large cohort of patients with detailed imaging findings, with a comprehensive tumor registry to permit the quantification of the risk of cancer associated with specific findings. The results suggest that the number of biopsies can be reduced by up to 90%, with a relatively small impact on cancer detected. The results are being rapidly embraced by endocrinologists, surgeons and radiologists.*

11) **Smith-Bindman et al Ultrasound versus Computed Tomography for Suspected Nephrolithiasis NEJM. 2014.** *This 15-center randomized comparative effectiveness study assessed whether ultrasound or CT should be the first imaging test in patients with suspected kidney stones. The study is unique in using a rigorous randomized trial design to assess a diagnostic imaging test, and in assessing a broad range of outcomes other than diagnostic accuracy. Emergency department patients with abdominal pain and suspected nephrolithiasis*

were randomly assigned to one of three arms for imaging: ultrasound performed by an emergency medicine physician, ultrasound provided by a radiologist, or computerized tomography (CT). No significant differences were observed over the next 6 months in rates of severe serious adverse events (SAEs), related SAEs, or total SAEs, or ED or hospital admission rates at 7 or 30 days; however, initial imaging with ultrasound was associated with lower 1 day and 6-month cumulative radiation exposures than initial imaging with CT. The manuscript was cited 45 times based on SCOPUS accessed in 2015

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Current Exposure to Computed Tomography Imaging in US Integrated Health Care Systems, presented at the Conference on Radiation in Health by the Radiation Research Society, Kona, HI, 10/15-17, 2016

Current CT doses from a Computed Tomography Dose Registry in Pediatric Patients, Presented at the American Academy of Pediatrics Annual Meeting, San Francisco, CA, 10/22-25/2017

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Practical Strategies for Optimizing Dose, A Dose of Reality

European Congress of Radiology, European Society of Radiology, 2018
An International Randomized Controlled Trial of Two Interventions for Reducing Doses for Computed Tomography (CT) Through Audit Feedback and Sharing Best Practices

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Exhibit B

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Exhibit C

Rebecca Smith-Bindman Compensation and Prior Testimony

Dr. Smith-Bindman's fees are \$1,000/hr. She has not testified in other cases during the previous four years.

Exhibit 57

Systematic Review and Meta-Analysis of the Association between Perineal Use of Talc and Risk of Ovarian Cancer

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20 **Abstract**

21 Over the past four decades, there has been increasing concern that perineal use of talc
22 powder, a commonly used personal care product, might be associated with an
23 increased risk of ovarian cancer.

24 **Objectives:** To systematically review all available human epidemiological data on the
25 relationship between perineal use of talc powder and ovarian cancer, with consideration
26 of other relevant experimental evidence.

27 **Methodology:** We identified 30 human studies for qualitative assessment of evidence,
28 including 27 that were retained for further quantitative analysis.

29 **Results:** A positive association between perineal use of talc powder and ovarian cancer
30 was found [OR: 1.28 (95% CI: 1.20 - 1.37)]. A significant risk was noted in Hispanics
31 and Whites, in women applying talc to underwear, in pre-menopausal women and in
32 post-menopausal women receiving hormonal therapy. A negative association was noted
33 with tubal ligation.

34 **Conclusion:** Perineal use of talc powder is a possible cause of human ovarian cancer.

35 **Keywords:** Talc; ovarian cancer; perineal; epidemiological studies; systematic review;
36 meta-analysis; toxicological studies.

1. Introduction

Ovarian cancer is a common gynecologic cancer among women in developed countries, occurring at low rates among young women but increasing with age [1]. The annual incidence rate of ovarian cancer during the period 2005 – 2009 was 12.7/100,000 women, varying by ethnicity. The majority of ovarian cancers are diagnosed at an advanced stage, with 61% having distant metastases at diagnosis. Hereditary risk factors for ovarian cancer, specifically BRCA1 gene mutations, increase the risk above 35 years of age by about 2-3%.

In recent decades, there has been increasing concern that perineal exposure to talc, a commonly used personal care product, might be associated with an increased risk of ovarian cancer. However, the data describing this association is somewhat inconsistent. Perineal application of talc among women varies by geographic location (Supplementary Material I), with prevalence of use generally higher in Canada, the US and the UK compared to Greece, China and Israel [2].

In order to better characterize the potential ovarian cancer risk associated with perineal use of talc, we conducted a systematic review and meta-analysis of peer-reviewed human studies on this issue. We also examined additional in-vitro or in-vivo toxicological studies, which shed light on possible biological mechanisms that might support an association between and ovarian cancer.

2. Materials and Methods

2.1. Literature Search and Identification of Relevant Human Studies

A comprehensive, multi-step search strategy was used to identify relevant studies on talc from multiple bibliographic databases, relevant national and international agencies and other grey literature sources (Supplementary Material II). Specifically, conducted a systematic search for all original studies involving human subjects that examined the association of genital/perineal use of talc powder and risk of ovarian cancer, including studies identified in a previous review by Berge et al. [3]. This review followed the PRISMA guidelines, and more specific guidance provided by the Cochrane Collaboration [4] (see Supplementary Material II for details).

Included studies were individually evaluated and scored by two reviewers (MT and NF), as detailed in the Table 1 and Supplementary Material XI. Studies included in previous reviews by both Berge et al. [3] and Penninkilampi et al [5] are compared in Supplementary Material I.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) [6], as detailed in Supplementary Material IV. We used a cut-off point of 7+ stars to represent studies of higher quality.

2.2. Literature Search and Identification of Relevant Non-Human Studies

We conducted a (non-systematic) review of relevant non-human studies identified in three major bibliographic databases to identify potentially relevant animal

and in vitro studies (Supplementary Material V). Only studies that focused on perineal exposure to talc powder were included. For outcomes, studies that focused on any type of cancer including ovarian cancer and perineal exposure were considered. All retrieved studies were examined for relevance, reliability and overall quality using the Klimisch scoring system [7, 8] (Supplementary Material VII, VIII and IX).

Studies are classified into one of the following four categories of reliability: 1) reliable without restriction, 2) reliable with restrictions, 3) not reliable and 4) not assignable. Additionally, category (5) is assigned to special studies focusing on pharmacologic or mechanistic investigations.

2.3. Hazard Characterization

Epidemiological studies included in the systematic review were qualitatively assessed to examine their potential to inform a weight of evidence analysis. Findings from these studies were evaluated with respect to study design, exposure and outcome ascertainment, as well as potential sources of bias and confounding.

Animal studies were evaluated for evidence on the association between perineal application of talc and ovarian cancer. Additional information on mechanism of action and toxicokinetics derived from in-vitro and in-vivo studies was used in evaluating biological plausibility.

We evaluated the overall weight of scientific evidence by performing a qualitative evaluation of the findings collected from epidemiological studies as well as non-human studies, using the Hill criteria [9].

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99

100 **2.4. Quantitative Meta-Analysis**

101 We conducted a meta-analysis of the risk of ovarian cancer in relation to perineal
102 use of talc using quantitative risk estimates reported in 27 original studies, comprising
103 three cohort studies and twenty-four case-control studies (included in Table 1). Studies
104 that had analyzed overlapping study populations were assessed on a case-by-case
105 basis for inclusion into the meta-analysis. The level of detail in the reported findings,
106 including sample size and publication date, were considered when deciding which study
107 to include in the case of overlap (Supplementary Material XIV).

108 Maximally adjusted odds ratios (ORs), hazard ratios (HRs) or relative risks (RRs)
109 – measures that are largely comparable because of the relatively low rate of occurrence
110 of ovariaion cancer – were extracted from the original studies. Details of the meta-
111 analytic methods are provided in Supplementary Material XIV.

112

113

114 **Table 1: Characteristics and overall findings of all included studies (N=30).**

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Case-control studies						
Booth et al.* (1989), UK [10]	235/451	Range: 20-65 Mean: 52.4 (cases); 51.4 (controls)	Frequency	No trend found	Possible association with >weekly use.	5
Chang and Risch (1997), Canada [11]	450/564	Range: 35-79 Mean: 57.2 (cases); 57.5 (controls)	Ever use Frequency Duration Time of use Type of use	Possible exposure- response with frequency and duration of use	Positive association	7

¹ Newcastle-Ottawa Scale (NOS) score for each of the listed studies as assessed in our review

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response	Overall Author	NOS ¹
				Assessment	Conclusion	
Pelvic surgery						
Histology						
Chen et al.* (1992), China [12]	112/224	Mean: 48.5 (cases); 49.0 (controls)	Ever use;	No trend analysis	Positive association	6
				conducted	with use >3 months	
Cook et al. (1997), USA [13]	313/422	Range: 20-79	Ever use	No trend found	Positive association.	7
			Duration			
			Type of use			
			Histology			
			Lifetime applications			
Cramer et al. (1982), USA [14]	215/215	Range: 18-80	Ever use	No trend analysis	Positive association	6
		Mean ± SD: 53.2 ±	Type of use	conducted		
		1.0 (cases); 53.5 ±	Pelvic surgery			
		1.0 (controls)				

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Cramer et al. (2016), USA [15]	2,041/2,100	Range: 18-80	Ever use; Frequency; Duration; Type of use; Histology; Type of powder; Pelvic surgery; Ethnicity; Age at first use; Time since last exposure;	Significant trend for years since exposure, frequency and duration of use, and number of lifetime applications	Positive association	7
Gates et al. (2008), USA [16]	New England Case Control (NECC): 1,175/1,202 Nurses' Health	Mean \pm SD: 51 \pm 13 (NECC); Mean \pm SD: 51 \pm 8 (NHS)	Ever use; Frequency; Time since last exposure;	Significant trend for frequency of use	Positive association	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Study (NHS):						
	210/600					
Godard et al. (1998), Canada [17]	153/152	Mean: 53.7	Ever use; Sporadic/familial	No trend analysis conducted	No association	5
Green et al. (1997), Australia [18]	824/860	Range: 18-79	Ever use; Pelvic surgery;	No trend found	Positive association	7
Harlow et al. (1989), USA [19]	116/158	Range: 20-79	Ever use; Type of use; Type of powder;	No trend analysis conducted	No association	7
Harlow et al. (1992), USA [20]	235/239	Range: 18-76	Ever use; Frequency; Duration; Type of use;	Significant trend for monthly frequency of use 1960, women <50	Positive associations in certain subgroups (talc used before 1960, women <50	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
			Method of use;		years old, women	
			Histology;		with 1 or 2 live	
			Tumor grade;		births)	
			Type of powder;			
			Lifetime applications;			
			Age of first use;			
			Pelvic surgery;			
Hartge et al. (1983), USA [21]	135/171	Mean: 52.1 (cases); 52.2 (controls)	Ever use;	No trend analysis conducted	No association	5
Kurta et al. (2012), USA [22]	902/1,802	Range: No range reported (age 25+)	Ever use;	No trend analysis conducted	Positive association	6
Langseth & Kjaerheim (2004), Norway [23]	46/179	Not reported	Ever use,	No trend analysis conducted	No association	4

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Merritt et al. (2008), Australia [24]	1,576/1,509	Range: 18-79 Mean: 57.8 (cases); 56.4 (controls)	Ever use; Duration; Histology; Pelvic surgery; Age at diagnosis;	No trend found	Positive association strongest for serous and endometrioid subtypes.	7
Mills et al. (2004), USA [25]	249/1,105	Mean \pm SD: 56.6 (cases); 55 (controls)	Ever use; Frequency; Duration; Year of first use; Histology; Pelvic surgery; Time of use; Tumor behavior; Cumulative use;	No trend found	Positive association for invasive and serous invasive tumors.	6

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Moorman et al. (2009), USA [26]	African- American: 143/189; White 943/868	Range: 20-74	Ever use; Ethnicity;	No trend analysis conducted	No association	6
Ness et al. (2000), USA [27]	767/1,367	Range: 20-69	Ever use; Duration; Method of use;	No trend found	Positive association for any method of use.	6
Rosenblatt et al. (1992), USA [28]	77/46 (analyzed)	Range: $\leq 30 - 80 \geq$	Ever use; Duration; Type of use; Pelvic surgery;	Positive trend for duration of use since tubal ligation	Possible association	4
Rosenblatt et al. (2011), USA [29]	812/1,313	Range: 35-74	Ever use; Lifetime number of applications; Duration;	No trend found	Possible association	7

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Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Schildkraut et al. (2016), USA [30]	584/745	Range: 20-79	Year of first use;			
			Age of first use;			
			Age of last use;			
			Time of use;			
			Type of use;			
			Histology;			
			Ever use;	Significant trend with frequency and duration of use, and number of lifetime applications	Positive association	8
Tzonou et al. (1993), Greece [31]	189/200	Range: <70	Ever use;	No trend analysis conducted	No association	5

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Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Whittemore et al. (1988), USA [32]	188/539	Range: 18-74	Ever use; Frequency; Duration; Type of use; Pelvic surgery;	No trend found	Could neither implicate nor exonerate talc as an ovarian carcinogen	4
Wong et al. (1999, 2009), USA [33, 34]	462/693	Mean: 54.9	Ever use; Type of use; Duration; Pelvic surgery;	No trend found	No association	4
Wu et al. (2015), USA [35]	1,701/2,391	Range: 18-79	Ever use; Ethnicity;	No trend analysis conducted	Positive association among Hispanics and non-Hispanic whites, but not African Americans.	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Wu et al. (2009), USA [34]	609/688	Range: 18-74	Ever use; Frequency; Duration; Type of use; Histology; Time of use; Cancer stage;	Significant trend for frequency and duration of use, and number of lifetime applications	Positive association	7
Cohort studies						
Gates et al. (2010)*, USA [36]	797/108,870	Range: 30-55	≥/week vs <1/week; Histology;	No trend analysis conducted	Possible association that varies by histological subtype. No association with mucinous tumors.	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS ¹
Gertig et al. (2000), USA [37]	307/78,630	Range: 30-55 (at cohort entry)	Ever use; Frequency; Histology; Race;	No trend found	Possible association (modest increase for serous invasive subtype)	5
Gonzalez et al. (2016), USA [38]	154/41,654	Range: 35-74 Median: 57.8	Ever use; Time of use;	No trend analysis conducted	No association	6
Houghton et al. (2014), USA [39]	429/61,285	Range: 50-79 Mean: 63.3	Ever use; Duration; Type of use; Histology;	No trend found	No association	7

* Study assessed for qualitative evidence but not included in the meta-analysis

115

3. Results

3.1. Evidence from Human Studies

The multiple database search for original human studies yielded 656 references. Although grey literature search yielded another 477 references, only 5 were judged relevant to the present analysis. Automatic followed by manual removal of duplicates identified 282 references for screening and review.

Multi-level screening and full-text examination resulted in the inclusion of 30 studies for further qualitative/quantitative analyses (Supplementary Materials X and XI). A detailed PRISMA flow diagram is shown in Figure 1 [40]. Key characteristics of the included 26 case-control studies and four cohort studies are summarized in Table 1.

Twenty-one of the thirty studies were carried out in the USA, with the remaining studies conducted in Europe (n=4), Canada (n=2), Australia (n=2) and China (n=1). Forty percent (n=12) of the studies were relatively recent, published in the last decade, with the remaining studies published between 1982 and 2006. The study populations generally included adult women. Several studies analyzed data from populations initially recruited for other purposes, such as the Nurses' Health Study (NHS) [15, 36, 37] and Women's Health Initiative (WHI) [39].

The number of ovarian cancer patients analyzed varied from as few as 46 cases [23] to 22,041 cases [15]. Twenty-seven out of the 30 included studies assessed the association between ever use of perineal talc use and ovarian cancer. Subgroup

analyses examining the effect of frequency and duration of use, type of use, period of
use and other factors varied among these studies (Table 1).

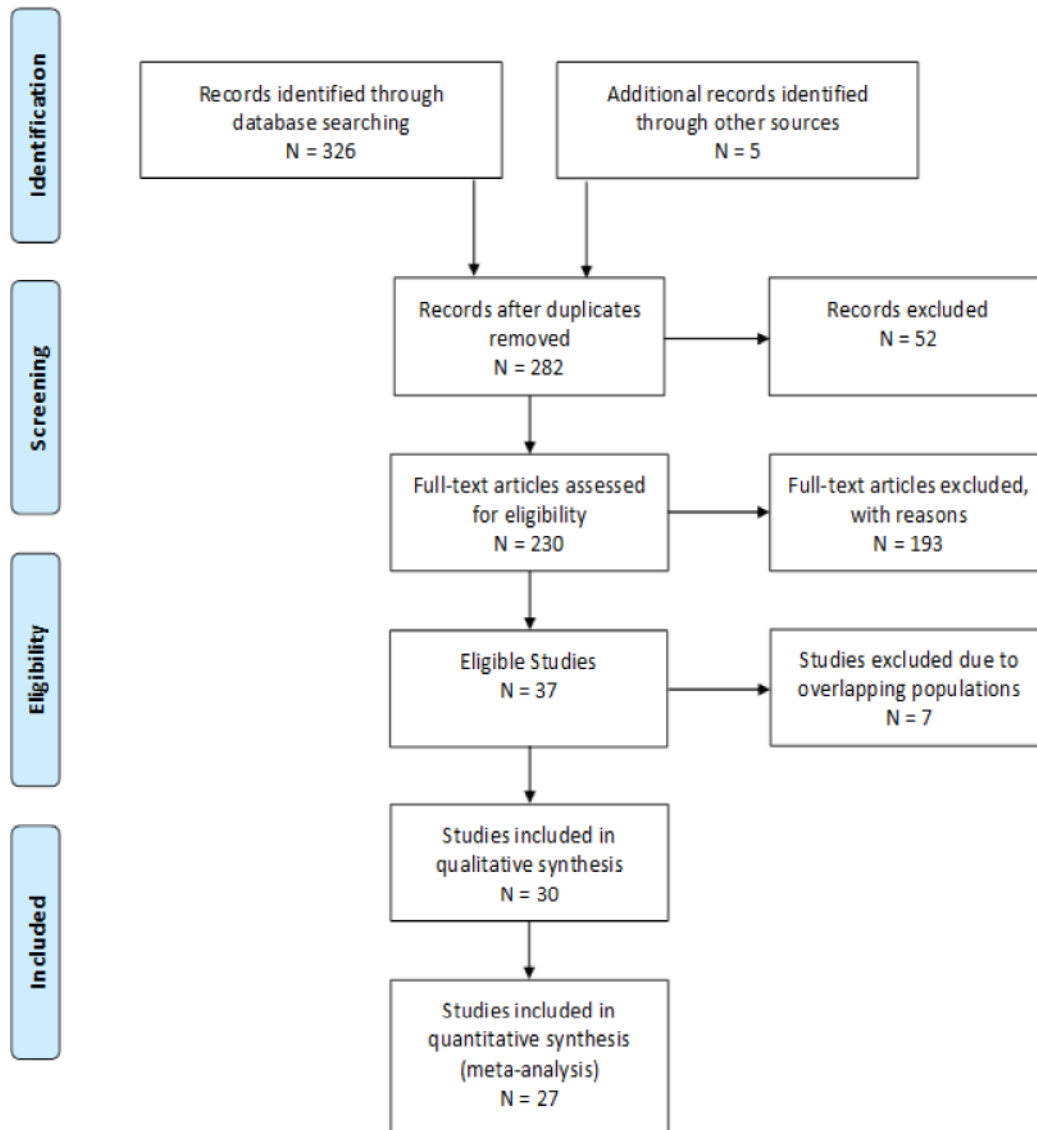


Figure 1: PRISMA Flow Diagram

Sixty three percent (n=19) of the studies concluded the presence of a positive
association between perineal exposure to talc powder and ovarian cancer risk [10-16,

18, 20, 22, 24, 25, 27-30, 34-36]. Ten studies concluded the absence of an association [17, 19, 21, 23, 26, 31, 33, 37-39]. Only one study could not reach a clear conclusion on the presence or absence of an association [32]. Many of the included studies reported variability in some of the analyzed subgroups regarding possible association between exposure to talc powder and risk of ovarian cancer. Supplementary Material X presents the findings and details of all the studies included in the analysis, while Supplementary Material XI summarizes the strengths and limitations of each of these studies as identified by the original study authors and by us.

3.2. Evidence from Non-Human studies

After removal of duplicates, the bibliographic database searches on non-human studies initially yielded 1,165 references. The 51 retained animal studies focusing on the carcinogenicity of talc, mechanism of action, and toxicokinetics are summarized in Supplementary Material XII.

3.3. Hazard Characterization

3.3.1. Evidence from Human Studies

The case-control studies generally included adult women participants. Cases were commonly selected from registries or hospital records, and included all eligible subjects within a specific geographic region and diagnosed with ovarian cancer within a predetermined time period. Controls were generally matched to cases by age and residence. All the included studies compared the risk of ovarian cancer in ever vs never

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users of talc (perineal application). However, several of the studies also included subgroup analyses to examine the potential effect of frequency of use, duration of use, tumor histology, ethnicity, method of use, lifetime number of applications, year of first use, and menopausal status. Some authors concluded that the risk of ovarian cancer is limited to [or stronger in] certain subgroups (weekly talc users, premenopausal women) or for specific histology types (notably serous tumors).

Studies reported effect estimates adjusted for a variety of potential confounders (see detailed tables in Supplementary Material X & XI). Age and parity were considered the two most important variables that could introduce potential bias, based on prior literature: few studies reported findings that were not adjusted for these two variables. As many of the studies only reported on the ovarian cancer risk assessing only one exposure category (comparing only ever vs never users of talc), exposure-response analyses were not done in all studies. When conducted, findings from trend analyses were not consistent.

3.3.2. Evidence from Non-Human Studies

The following aspects were considered in the weight of evidence assessment of ovarian cancer and perineal exposure to talc:

- hazards arising from the physical and chemical properties of talc, including potential structure-activity relationship indicative of carcinogenic potential;
- the toxicokinetics of talc and the ability to migrate from the perineal area to ovaries and quantity at the actual target site (the tissue dose);

- evidence on ovarian cancer reported in animal studies; and
- findings from in vitro studies suggestive of mechanism of action of carcinogenic effect.

While the data from the animal studies considered various routes of talc administration are inconsistent [41-46], there are observations from in vivo and in vitro studies which support the potential for local carcinogenic action of talc on fallopian, ovarian and peritoneal epithelium [27, 47-53].

The results from the *in vitro* studies are informative for mechanisms of action of possible carcinogenicity. Smith and colleagues [54] identified 10 key characteristics (KCs) commonly exhibited by established human carcinogens.

Oxidative stress (KC 6) and inflammation (KC 5) in cell cultures induced by talc have been reported by several authors [48], corresponding to two of the 10 key characteristics (KCs) described by Smith et al. [54]. Several authors suggested additional potential mechanisms of action through cell proliferation (KC 10) and changes in gene expression, presumably facilitated by oxidative stress and dysregulated antioxidant defense mechanisms [49, 55].

Chronic perineal or vaginal exposures of animals to talc do not directly affect ovulation or steroidal hormone levels, but can induce chronic local inflammation, which has been suggested as a risk factor for ovarian cancer [56]. Mechanism of action studies suggested that talc can complex iron on the surface and disrupt iron homeostasis, associated with oxidant generation, macrophage distress and leukotriene

released by macrophages in the surrounding cells resulting in the inflammatory response which could act as a tumor promoter in both animals and humans [48, 50, 51].

The changes seen in cultured cells after exposure to talc [50, 51] are consistent with those inflammatory and proliferative processes in the lungs seen in laboratory animals after inhalation exposure in a 1993 study conducted by the US National Toxicology Program [47]. In female rats, hyperplasia of alveolar epithelium was associated with inflammatory response and occurred in or near foci of inflammation [47]. The severity of the fibrous granulomatous inflammation in the lungs increased with increased talc concentrations and exposure duration and a significant association was observed between inflammation and fibrosis in the lungs and the incidence of pheochromocytomas in this study [47]. Overall, the available experimental data suggest irritation, followed by oxidative stress and inflammation, may play be involved in local carcinogenic effects of talc in the ovaries.

Local inflammation of the epithelial ovarian surface in rats following by injection of a suspension of talc particles demonstrated the development of foreign body granulomas surrounding talc particles and large ovarian bursal cysts [53]. It is generally accepted that benign and malignant ovarian epithelial tumors arise from surface epithelium and its cystic derivatives, and surface epithelial cysts have a greater propensity to undergo neoplasia than does the surface epithelium itself [57]. Evidence of neoplasms of epithelial origin, nuclear atypia, or mitotic activity in the surface epithelium was not found in this study; however, focal areas of papillary changes in the surface epithelium consistent with the histological signs of premalignancy were observed in 40% of treated animals [53].

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Data on talc migration in the genital tract of animals is inconsistent, but could not exclude such possibility [58-61]. Some studies have reported lack of neutron-activated talc migration from the vagina to the ovaries in cynomolgus monkeys [58], but talc particles were identified in the ovaries of rats that received intrauterine instillation of talc [60]. Radioactivity was not found in the ovaries of rabbits dosed intravaginally with tritium-labelled talc, but was detected in cervix and fallopian tubes [59-61]. In studies in humans, Henderson and colleagues [62] examined tumor tissue of female patients with ovarian and cervical tumors. The authors detected talc particles in histological samples from 10 of 13 ovarian tumors, 12 of 21 cervical tumors and in 5 samples of 12 normal ovarian tissues [62].

Historically, the concern for talc carcinogenicity has been associated with its contamination by asbestos fibers (tremolite) [63], which is considered carcinogenic to humans [2]. Talc, including baby powder, available in the US, contains only U.S. Pharmacopeia (USP) grade pure talc [64]. Talcum powder has been asbestos-free since the 1976 where the specifications for cosmetic talc were developed [65].

3.3.3. Weight of evidence for carcinogenicity

Based on our evaluation of the weight of multiple lines of evidence, we concluded that perineal application of talc is a possible cause of ovarian cancer in humans. In 2010 the International Agency for Research on Cancer [2] categorized perineal use of talc-based body powder (not containing asbestos or asbestiform fibers) as “possibly carcinogenic to humans (Group 2B)” [66].

Table 2 summarizes the available evidence for the association of ovarian cancer with perineal application of talc, organized around the nine Hill criteria [9]. Additional details of this evaluation are given in Supplementary Material XIII.

Table 2: Summary of evidence for each of the Hill Criteria of causation, as applied to perineal application of talc and ovarian cancer

Criterion	Summary of Evidence
Strength of association	<ul style="list-style-type: none"> Out of the 30 epidemiological studies, six reported positive association of statistical significance with a risk value (relative risk or odds ratio) of 1.5 or greater None of the cohort studies (n=3) found statistically significant association
Consistency	<p>Fifteen out of thirty studies reported positive and significant associations reported in:</p> <ul style="list-style-type: none"> Different ethnicities (Caucasians, African Americans, and Latin Americans); Over four decades (1982 - 2016); Mostly in studies from the United States but also in other countries (Canada, Australia and China) Case-control studies but not in cohort studies
Specificity	<ul style="list-style-type: none"> Overall, the perineal talc exposure is specifically associated with cancer of the ovary and not other organs No evidence of other target organs (e.g., liver) being associated with perineal application of talc (via systemic exposure)

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Criterion	Summary of Evidence
	<ul style="list-style-type: none"> Thirteen studies included analyses by histologic type of ovarian cancer, and eight of them found a significant increase in the risk of serous ovarian cancer in talc users
Temporality	<ul style="list-style-type: none"> In all case-control studies reporting positive outcome, the participants recalled that exposure to talc preceded the reported outcome In cohort studies, the follow up period could have been inadequate (<15 years) to detect a potential association between talc exposure and ovarian cancer
Biological gradient (exposure-response)	<ul style="list-style-type: none"> About half of the epidemiological studies assessed only one level of talc exposure (ever vs never usage) Of the 12 studies reporting a positive association, six studies found significant exposure-response trend, particularly with medium and high frequency usage groups Regarding duration of use/exposure to talc, several studies reported the greatest risk in the 20+ years of use exposure group, followed by the 10-20 years' group, then the <10 years' group
Biological plausibility	<ul style="list-style-type: none"> Particles of talc appear to migrate into the pelvis and ovarian tissue causing irritation and inflammation Transport of talc via perineal stroma and presence in ovaries documented Chronic inflammatory response and alteration in local immunogenicity are possible mechanisms
Coherence	<ul style="list-style-type: none"> Results from talc epidemiology studies are coherent with the current knowledge on the risk factors for ovarian cancer (e.g., factors/physiological states associated with greater frequency and duration of ovulation are associated with increased risk of ovarian cancer)

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Criterion	Summary of Evidence
	<ul style="list-style-type: none"> Many (but not all) case-control studies reported lower risk of ovarian cancer in women who underwent pelvic surgery or tubal ligation (which disrupts the pathway and movement of talc from lower to upper genital tract) & suppressed ovulation
Experimental evidence	<ul style="list-style-type: none"> Perineal application of talc has not been tested in an animal model of ovarian cancer The single animal cancer bioassay with talc conducted by the US National Toxicology Program was only by the inhalation route Rodent models may be of limited relevance because of ovulations occurring only or mainly during the breeding season and the rarity of ovarian epithelial tumors in these animals and ovaries are variously enclosed in an ovarian bursa.
Analogy	<ul style="list-style-type: none"> Talc and asbestos are both silicate minerals Talc has been variably contaminated with asbestos (tremolite and anthophyllite; until 1976, talcum powders were only required to contain at least 90% mineral talc) The pleural and peritoneal mesotheliomas caused by asbestos are histologically similar to epithelial ovarian cancer associated with talc In animal models, asbestos induces ovarian epithelial hyperplasia similar to early epithelial tumors reported in women with past use of talc

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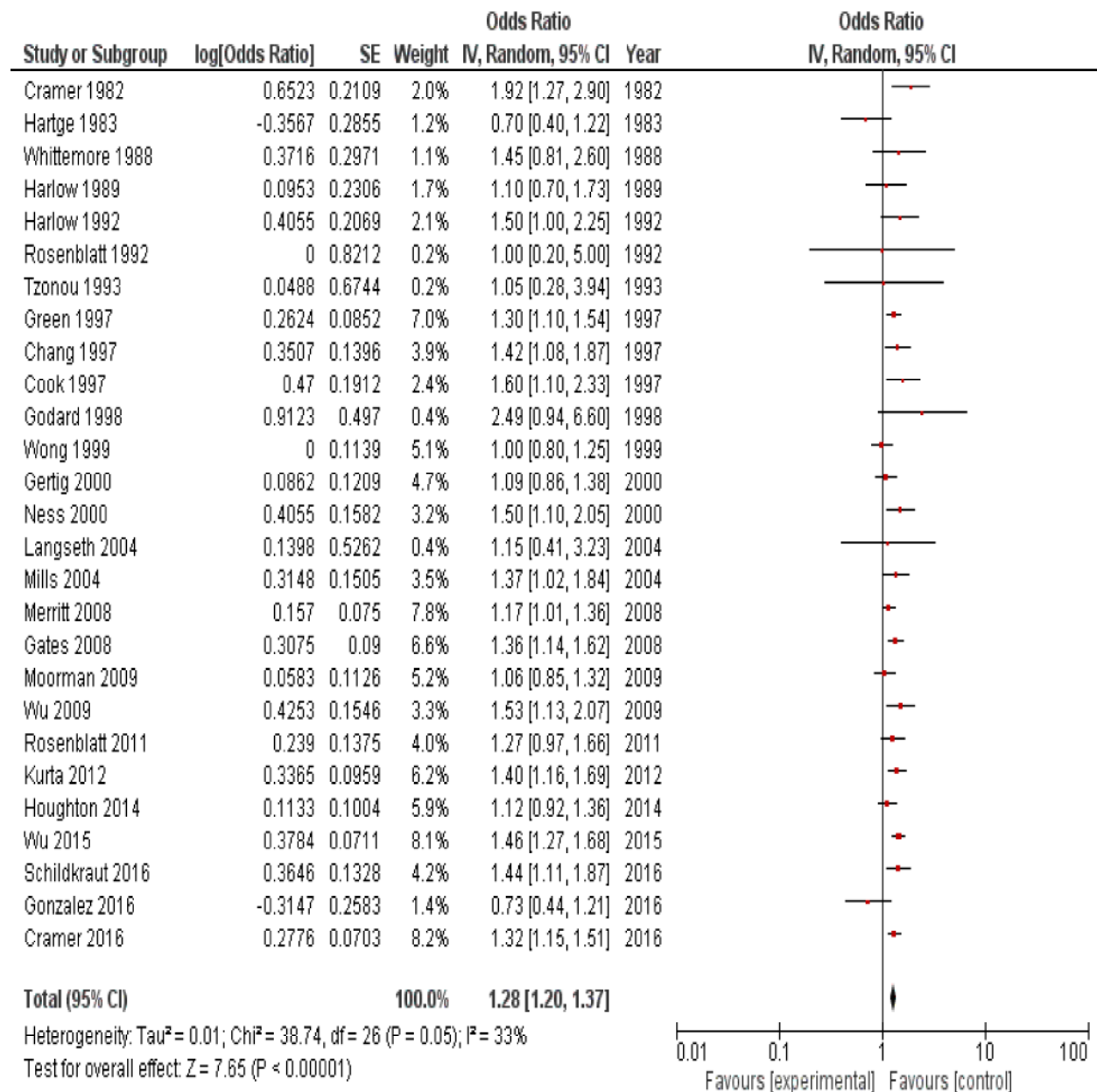
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261 **3.4. Meta-Analysis**

262 The use of genital talc was associated with a significant increase in the risk of
263 epithelial ovarian cancer, with an overall odds ratio [OR] based on our meta-analysis of
264 1.28 (95% confidence interval [CI]: 1.20 to 1.37 $P < 0.0001$, $I^2 = 33\%$), as presented in

265 Figure 2. This result is comparable to those of earlier meta-analyses conducted by other
266 investigators [3, 5, 67-69] as shown in Supplementary Material I.



267
268 **FIGURE 2: Forest plot of the meta-analysis results on perineal use of talc and**
269 **risk of ovarian cancer**

270

271 An increased risk is more apparent in Hispanics and Whites, in women applying
272 talc to underwear, in pre-menopausal women and post-menopausal women receiving
273 hormonal therapy, as well as for the serous and endometrioid types of ovarian cancer
274 (Table 3 and Supplementary Material XIV). A negative association was noted with tubal
275 ligation. Our analysis pooled risk estimates from 27 original studies including 3 cohort
276 studies and 24 case-control studies, spanning across four decades (1982-2016) and
277 including a total of 16,352 cases and 19,808 controls from different ethnicities.

278 In assessing heterogeneity among included studies, most subgroup analyses
279 reported an I^2 statistic ranging between 0%-40%, which will have only a minimal impact
280 on the analysis [4]. Only three subgroup analyses (ethnicity, menopausal state, and
281 pelvic surgery) reported an I^2 statistic of 77%-78%, where considerable heterogeneity
282 might have had an impact on the results [4]. (See Table 3 and Supplementary Material
283 XIV for a listing of I^2 statistic values for the different subgroup analyses)

284 Whereas case-control studies showed a significant increase in the risk of ovarian
285 cancer for ever vs never users of talc powder [OR: 1.32 (95% CI: 1.24 to 1.40), $P <$
286 0.00001, $I^2 = 22\%$], cohort studies failed to show a significant increase in risk [OR: 1.06
287 (95% CI: 0.9 to 1.25), $P = 0.49$, $I^2 = 17\%$]. Thirteen out of 24 case-control studies (54%)
288 showed a statistically significant association, whereas none of the 3 cohort studies
289 showed a significant overall association between ever vs never genital talc exposure
290 and risk of ovarian cancer.

Subgroup analysis by study quality ($NOS \geq 7$ vs $NOS < 7$) did not show any significant differences in the overall pooled risk estimate. Similarly, there were no differences among subgroup analysis conducted by decade of publication. A significant association was observed for population-based studies [OR: 1.34 (95% CI: 1.27 to 1.41), $P < 0.00001$, $I^2 = 0\%$], but for enlisting hospital-based controls [OR: 0.96 (95% CI: 0.78 to 1.17), $P = 0.66$, $I^2 = 0\%$].

We conducted influence analysis to examine the impact of individual studies on the results of our meta-analysis. No appreciable changes were observed regarding the overall association of perineal talc exposure and the risk of ovarian cancer in response to the exclusion of any one study. Detailed results from the influence analysis are provided (Supplementary Material XIV).

Subgroup analysis based on ethnicity indicated that Hispanic women using talc showed the most significant increase in risk of ovarian cancer [OR: 1.70 (95% CI: 1.17 to 2.47), $P = 0.005$, $I^2 = 0\%$], followed by White women [OR: 1.28 (95% CI: 1.10 to 1.49), $P = 0.001$, $I^2 = 56\%$]. African-American women showed a non-significant association with ovarian cancer in [OR: 1.67 (95% CI: 0.90 to 3.10), $P = 0.1$, $I^2 = 48\%$].

Analyzing exposure by frequency of talc use, talc exposure was stratified into three groups: high (once daily for >25 days/month), medium (once daily for 10–25 days/month) and low (once daily for 1– <10 days/month). The OR for the high-use group was higher in the high-use group compared to the other two groups (medium and low-use groups). Duration of talc use was stratified into three groups: <10 years, 10 – <20 years, and 20+ years. The overall odds ratio of the <10 years' group was lower than the

OR for the 10 – <20 years' group. On the other hand, the OR for the 20+ years' group was lower and not statistically significant. However, this OR was based on two studies that showed considerable heterogeneity ($I^2=75\%$). Examining the method of application of talc, application to the underwear subgroup had a statistically significant OR, which was the highest among all subgroups. Diaphragm use showed an expected, yet non-significant, negative association with ovarian cancer, which may be due to its action blocking the ascent of talc particles up the reproductive tract.

Pooled risk estimates were statistically significant for two histological types of ovarian cancer: serous tumors [OR: 1.38 (95% CI: 1.22 to 1.56), $P < 0.00001$, $I^2= 0\%$] and endometrioid tumors [OR: 1.39 (95% CI: 1.05 to 1.82), $P= 0.03$, $I^2= 2\%$]. The mucinous type showed a non-significant association [OR: 1.05 (95% CI: 0.85 to 1.29), $P= 0.41$, $I^2= 23\%$], while there were not sufficient studies to examine the other types of ovarian cancers. Regarding tumor behavior, there was no appreciable difference between invasive [OR: 1.38 (95% CI: 1.15 to 1.65), $P= 0.0004$, $I^2= 0\%$] and borderline [OR: 1.43 (95% CI: 1.08 to 1.89), $P= 0.01$, $I^2= 19\%$] grades of ovarian cancer. Borderline serous tumors showed slightly greater risk [OR: 1.39 (95% CI: 1.09 to 1.78), $P= 0.008$, $I^2= 0\%$] compared to the serous invasive grade [OR: 1.32 (95% CI: 1.13 to 1.54), $P= 0.0004$, $I^2= 24\%$], while both showed a significant association with perineal talc exposure. However, the mucinous tumors showed a non-significant association with talc exposure, with invasive grades being associated with a greater risk [OR: 1.34 (95% CI: 0.48 to 3.79), $P= 0.58$, $I^2= 70\%$] compared to the borderline grade [OR: 1.18 (95% CI: 0.76 to 1.82), $P < 0.46$, $I^2= 34\%$].

Among post-menopausal women, those receiving hormonal therapy showed the greatest risk [OR: 2.28 (95% CI: 1.72 to 3.01), $P < 0.00001$, $I^2 = 0\%$], followed by pre-menopausal women [OR: 1.42 (95% CI: 1.16 to 1.75), $P = 0.0008$, $I^2 = 0\%$], and then post-menopausal women not receiving hormonal therapy [OR: 1.05 (95% CI: 0.84 to 1.32), $P = 0.66$, $I^2 = 25\%$]. This subgroup analysis suggests that hormonal factors, especially estrogens influence the risk of developing ovarian cancer among postmenopausal women who have perineal talc exposure.

Women with prior ligation of the Fallopian tubes showed a significant reduction in risk [OR: 0.64 (95% CI: 0.45 to 0.92), $P = 0.02$, $I^2 = 19\%$] against ovarian cancer compared to hysterectomy [OR: 0.89 (95% CI: 0.54 to 1.46), $P = 0.65$, $I^2 = 61\%$], whereas both surgeries combined showed no effect [OR: 1.06 (95% CI: 0.78 to 1.42), $P = 0.72$, $I^2 = 61\%$]. This might be attributed to the fact that tubal ligation is usually performed at an earlier age, thus preventing entry of talc into the reproductive tract earlier and prolonged exposure to talc, compared to hysterectomy that is performed later in life where a higher exposure has already taken place. In a recent meta-analysis [70], the authors reported a negative association of tubal ligation (27 studies) and hysterectomy (15 studies) with the risk of ovarian cancer: this negative association was more apparent in women who had the surgery at an earlier age. A highly plausible mechanism for this association, as suggested by the authors, involves blocking of ascent of agents such as talc to the ovaries.

A summary of results of our meta-analysis is shown in Table 3. Forest plots of all sub-group analyses are provided in Supplementary Material XIV.

357

358

359 **Table 3: Results of the subgroup analysis of talc exposure and ovarian cancer**

Outcome or Subgroup	Studies	Effect Estimate [95% CI]	Heterogeneity I^2 Statistic [p-value]
1. Talc use			
Ever vs. Never	27	1.28 [1.20, 1.37]	33% [< 0.00001]
Ethnicity	3		77% [0.08]
<i>African Americans</i>	3	1.67 [0.90, 3.10]	48% [0.10]
<i>Hispanics</i>	2	1.70 [1.17, 2.47]	0% [0.005]
<i>Whites</i>	3	1.28 [1.11, 1.49]	56% [0.001]
<i>Asians</i>	1	0.04 [0.01, 0.16]	N/A
2. Study Assessment			
2.1. Study Design	27		33% [< 0.00001]
<i>Case-Control</i>	24	1.32 [1.24, 1.40]	22% [< 0.00001]
<i>Cohort</i>	3	1.06 [0.90, 1.25]	17% [0.49]
2.2. Type of Controls	24		22% [< 0.00001]
<i>Hospital-based</i>	4	0.96 [0.78, 1.17]	0% [0.66]
<i>Population-based</i>	19	1.34 [1.27, 1.41]	0% [< 0.00001]
<i>Combined</i>	1	1.45 [0.81, 2.60]	N/A
2.3. Quality Score (NOS)	27		33% [< 0.00001]
<i>NOS ≥ 7</i>	12	1.32 [1.25, 1.40]	0% [< 0.00001]
<i>NOS < 7</i>	15	1.21 [1.05, 1.39]	47% [0.009]
2.4. Publication Year	27		33% [< 0.00001]
<i>1980-1989</i>	4	1.23 [0.81, 1.88]	66% [0.33]
<i>1990-1999</i>	8	1.30 [1.13, 1.50]	24% [0.0003]
<i>2000-2009</i>	8	1.25 [1.14, 1.37]	18% [< 0.00001]
<i>2010 and beyond</i>	7	1.31 [1.18, 1.45]	44% [< 0.00001]
3. Talc Exposure			
3.1. Frequency of Use	7		35% [< 0.00001]
<i>Low</i>	5	1.22 [0.96, 1.54]	54% [0.10]
<i>Medium</i>	2	1.22 [0.98, 1.53]	0% [0.08]
<i>High</i>	7	1.39 [1.22, 1.58]	23% [< 0.00001]
3.2. Duration of Use	6		5% [0.0008]
<i><10 Years</i>	5	1.22 [1.03, 1.45]	0% [0.02]

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Outcome or Subgroup	Studies	Effect Estimate [95% CI)	Heterogeneity I^2 Statistic [p-value]
10 - <20 Years	2	1.42 [1.02, 1.99]	0% [0.04]
20+ Years	2	1.19 [0.71, 1.98]	75% [0.51]
3.3. Method of Use	13		52% [0.001]
Sanitary Napkin	11	1.12 [0.91, 1.39]	50% [0.29]
Diaphragm	10	0.87 [0.72, 1.05]	25% [0.14]
Underwear	2	1.70 [1.27, 2.28]	0% [0.0004]
Male Condom	3	0.99 [0.73, 1.32]	0% [0.92]
4. Tumor Histology			
4.1. Tumor Histology	8		23% [< 0.00001]
Serous	7	1.38 [1.22, 1.56]	0% [< 0.00001]
Mucinous	5	1.05 [0.85, 1.29]	23% [0.41]
Endometrioid	6	1.39 [1.05, 1.82]	2% [0.03]
Clear Cell	1	0.63 [0.15, 2.65]	
5. Tumor Behavior			
5.1. All Grades	4		0% [< 0.00001]
All Invasive	3	1.38 [1.15, 1.65]	0% [0.0004]
All Borderline	4	1.43 [1.08, 1.89]	19% [0.01]
5.2. Serous	5		0% [< 0.00001]
Serous Invasive	5	1.32 [1.13, 1.54]	24% [0.00004]
Serous Borderline	3	1.39 [1.09, 1.78]	0% [0.008]
5.3. Mucinous	3		38% [0.40]
Mucinous Invasive	2	1.34 [0.48, 3.79]	70% [0.58]
Mucinous Borderline	3	1.18 [0.76, 1.82]	34% [0.46]
5.4. Endometrioid	1		N/A
Endometrioid Invasive	1	1.38 [1.06, 1.80]	
5.5. Clear Cell	1		N/A
Clear Cell Invasive	1	1.01 [0.65, 1.57]	
6. Modifiers			
6.1. Menopausal State	2		78% [0.007]
Pre-menopausal	2	1.42 [1.16, 1.75]	0% [0.0008]
Post-Menopausal (HT)	2	2.28 [1.72, 3.01]	0% [< 0.00001]
Post-Menopausal (no HT)	2	1.05 [0.84, 1.32]	25% [0.66]

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Outcome or Subgroup	Studies	Effect Estimate	Heterogeneity I^2
		[95% CI)	Statistic [p-value]
6.2. Pelvic Surgery	7		78% [0.35]
<i>Tubal Ligation</i>	3	0.64 [0.45, 0.92]	19% [0.02]
<i>Hysterectomy</i>	4	0.89 [0.54, 1.46]	61% [0.65]
<i>Combined</i>	4	1.06 [0.78, 1.42]	61% [0.72]

* **NOS:** Newcastle-Ottawa Scale for quality scoring of observational studies

** **Low:** Once daily for 1 – <10 days/month; **Medium:** Once daily for 10 –25 days/month; **High:** Once daily for >25 days/month

3.5. Exposure-Response Assessment

The effect of increasing frequency or duration of perineal use of talc and the risk of ovarian cancer was assessed in the majority of the studies included in this review. Conflicting findings were reported on the nature of the exposure-response relationship: 11 studies concluded that there is no exposure-response, five studies reported a significant positive trend with either frequency or duration of talc use, and two studies concluded that there might be an exposure-response. The remaining twelve studies did not perform or report on trend analyses.

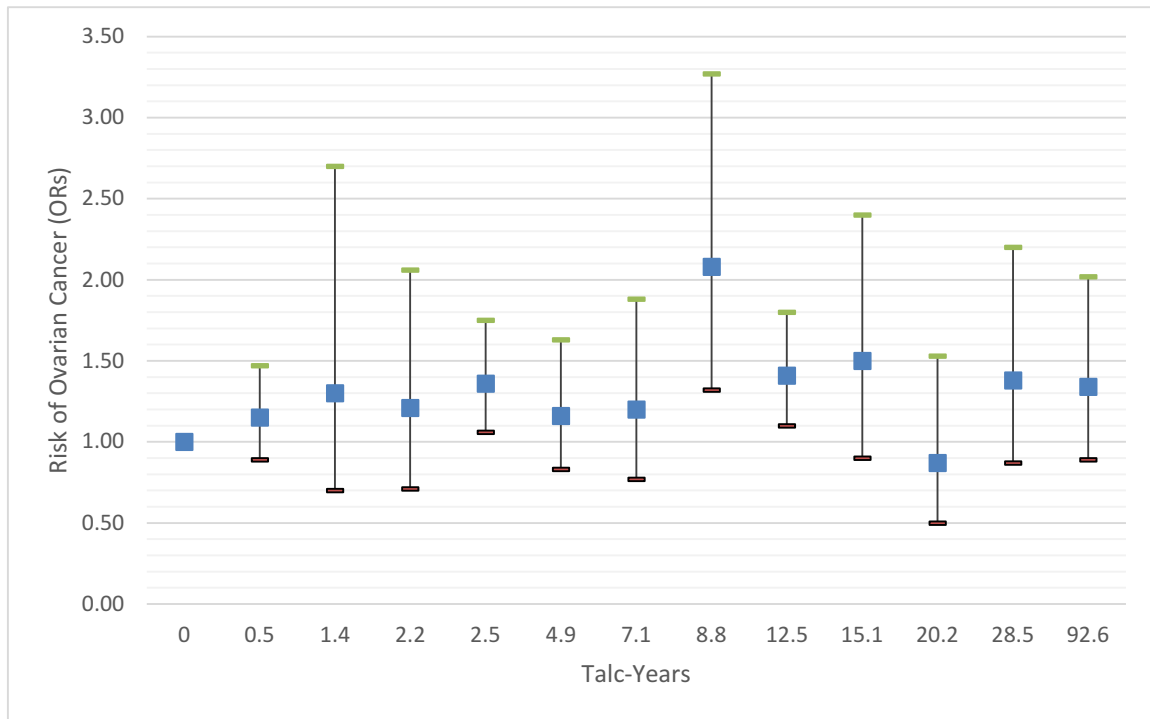
Findings from the seven studies that indicated a potential increased risk of ovarian cancer associated with increasing use of talc are presented in Table 4. The study by Cramer et al. [15] provides the strongest evidence of an exposure-response relationship and could be considered as a key study for exposure-response assessment. The data used in this study were generated from the Nurses' Health Study

originally conducted by Belanger et al. [71], a well-designed high quality cohort study of the factors affecting women's health. The results of this study show an increased risk of ovarian cancer at the three highest exposure categories in this study, with the risk at the lowest exposure level [OR: 1.15 (95% CI: 0.89 to 1.47)] being numerically, although not significantly, elevated. Other studies in Table 4 have provided findings in support of an exposure response based on increasing number of talc applications [20, 30, 34].

In order to permit more direct comparisons of the exposure-response findings from these studies, and whenever the original study data permits, we standardized exposure measurements into talc-years as shown in Figure 3. Data points were selected from studies after excluding potential data points that are lacking precise information on the level of exposure to talc. The mid-point of the exposure categories in the exposure-response studies was used for exposure-response assessment.

Overall, the graphical results shown in this Figure 3 suggest a possible increasing trend in ovarian cancer risk with increasing cumulative exposure to talc; however, there is also a high degree of uncertainty surrounding many of the individual risk estimates. (A formal statistical test for trend was not attempted because of the high degree of heterogeneity among studies noted previously in our meta-analysis discussed in section 3.4.)

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400 **Figure 3: Ovarian cancer risk estimates at increasing levels of exposure to talc, as**
401 **reported from multiple studies**

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Table 4: Summary of studies that reported ORs for increasing number of lifetime perineal talc applications

Study	Stratification	Reported Exposure-Response Strata	aOR*	95% CI
Schildkraut et al. (2016) [30]	Lifetime genital powder	<3,600 applications, any genital use vs (never use)	1.16	[0.83, 1.63]
		>3,600 applications, any genital use vs (never use)	1.67	[1.23, 2.26]
Whittemore et al. (1988) [32]	Overall trend	Overall trend for 30 uses per month	1.3	[0.88, 1.92]
Wu et al. (2009) [34]	By total times of talc use	≤ 5,200 times vs nonuse	1.2	[0.77, 1.88]
		5,201 – 15,600 times vs nonuse	1.38	[0.87, 2.20]
		15,601 – 52,000 times vs nonuse	1.34	[0.89, 2.02]
		> 52,000 times	1.99	[1.34, 2.96]
Mills et al. (2004) [25]	By cumulative use	First quartile (lowest exposure)	1.03	[0.59, 1.80]
		Second quartile	1.81	[1.10, 2.97]
		Third quartile	1.74	[1.11, 2.73]
		Fourth quartile (highest exposure)	1.06	[0.62, 1.83]
Rosenblatt et al. (2011) [29]	By lifetime number of applications of perineal powder after bathing	1-1,599 applications	1.21	[0.71, 2.06]
		1,600-4,799 applications	2.08	[1.32, 3.27]
		4,800-9,999 applications	0.87	[0.50, 1.53]
		≥10,000 applications	0.87	[0.48, 1.57]
Cramer et al. (2016) [15]	By total genital applications	≤360 total genital applications	1.15	[0.89, 1.47]
		361-1,800 total genital applications	1.36	[1.06, 1.75]
		1,801-7,200 total genital applications	1.41	[1.10, 1.80]
		>7,200 total genital applications	1.39	[1.11, 1.75]
Harlow et al. (1992) [20]	Total Lifetime Perineal Applications*	< 1,000 applications	1.3	[0.7, 2.7]
		1,000 - 10,000 applications	1.5	[0.9, 2.4]
		>10,000 applications	1.8	[1.0, 3.0]

* aOR: adjusted odds ratio

** 10,000 applications are equivalent to daily use for 30 year

4. Discussion

The present analysis of the association between perineal use of talc powder and ovarian cancer risk considered four decades of scientific work exploring the epidemiological associations and non-human studies. The motivation for this review is based on two questions: what do human epidemiology studies of perineal talc exposure reveal about potential ovarian carcinogenicity, and what do in-vitro and in-vivo studies suggest about potential mechanisms of toxicity?

A systematic review of the human epidemiology studies was conducted to address the first question. Thirty observational epidemiologic studies were identified and assessed for quality using the NOS [6]. In parallel with the review of human epidemiological evidence, a (non-systematic) review of evidence exploring in vitro and in vivo toxicology data on talc was conducted to explore how talc might produce biological changes. This latter review provides some insights concerning possible mechanisms of talc toxicity, including oxidative stress, immune system alterations and inflammatory responses. However, it also indicates that talc is not genotoxic. In total, the epidemiology studies suggest that perineal exposure to talc powder is a possible human ovarian carcinogen but there are concerns that the actual exposure experienced by these women over the past 40-50 years is not well understood. As reported by Langesth and colleagues [67], there had been some concern that asbestos-contaminated talc powder that was produced prior to 1976 might have been a confounder; however, the similarity of findings between studies published prior to and after this point suggests asbestos contamination does not explain the positive association between perineal use of talc powder and risk of ovarian cancer [25, 27].

Human observational studies have inherent limitations that could bias the findings. Potentially important sources of bias reported in the included studies include: 1) selection bias due to low response rates from cases and controls or from limiting subjects to English-speaking women of two specific races, and 2) exposure misclassification due to recall bias inherent in case control studies. Other limitations included small sample sizes in some studies, small numbers of subjects in subgroup analyses, lack of information on duration of talc use in many studies that only compared ever vs never users, as well as lack of information on the talc content of the different brands of genital powders used. In two of the three cohort studies, the follow-up period between exposure assessment and end of study could have been inadequate to detect a potential association between talc exposure and ovarian cancer. Houghton et al. [39] reported a mean follow up of 12.4 years, while Gates et al. [36] followed a cohort of women for 24 years. However, Gertig et al. [37] and Gonzalez et al. [38] noted that one of their main limitations is the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and ovarian cancer. For example, studies of smoking and ovarian cancer suggest that follow-up periods as long as four decades improve recognition of the carcinogenic effects of smoking [72]; longer follow up periods may also improve characterization of the association between talc and ovarian cancer. In this regard, the minimum latency period for radiation-induced ovarian cancer among Hiroshima atomic bomb survivors has been reported to range from 15 to 20 years [73, 74]. Common strengths reported in most studies were the selection of population controls in many of the case control studies and having relatively large sample sizes that allowed a multitude of stratified analyses.

Effect estimates in this meta-analysis were pooled from 24 case control studies and 3 cohort studies, and refer to ever vs never use of perineal talc. Pooling by study design showed a notably higher risk estimate for case-control [OR: 1.32 (95% CI: 1.24 to 1.40), $P < 0.00001$, $I^2 = 22\%$] compared to cohort studies [OR: 1.06 (95% CI: 0.9 to 1.25), $P = 0.49$, $I^2 = 17\%$]. Although the reasons for this are unclear, the difference could potentially be due to issues relating to latency, study power, or exposure misclassification.

Although cohort study designs are efficient for examining diseases with a long latency period, it is essential that the period between talc exposure and the cancer diagnosis be sufficiently long. Gonzalez et al. [38] suggested that the latency period for ovarian cancer is between 15 to 20 years. In the cohort studies included in this review, Houghton et al. [39] reported a mean follow up of 12.4 years while Gates et al. [36] followed a cohort of women for 24 years. Gertig et al. [37] and Gonzalez et al. [38] noted that one of their studies' main limitations was the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and ovarian cancer.

In addition, cohort studies included may have been underpowered to detect an odds ratio (relative risk) of 1.3 estimated from the case control studies. This was noted by Narod et al. [75], who suggest that cohorts of at least 200,000 women would be needed to reach statistical significance if the true odds ratio is 1.3. The cohort studies included in this review included much smaller cohort sizes, ranging between 41,654 and 78,630 women.

Finally, in cohort studies, talc exposure was assessed at cohort entry and was used as a measure of chronic talc use during follow up. It is possible that women who were not exposed to perineal talc at the time of cohort entry began using talc at a later time, and vice versa, possibly introducing non-differential misclassification of exposure, which could bias the risk estimate towards the null value of unity. Conversely, in the presence of differential exposure misclassification, a bias away from the null hypothesis could accentuate differences between the cohort and case-control studies.

4.1. Exposures and outcomes

All epidemiological studies included in our review evaluated the association between the perineal application of talc and subsequent diagnosis of ovarian cancer. Perineal vs body exposure is an important distinction, as the movement of talc is thought to follow an ascending path from the perineum through the vagina, uterus and fallopian tubes to the ovarian (as well as fallopian tube and peritoneal) epithelium.

Ovarian cancer is a common gynecologic malignancy in developed and developing countries. Risk factors for ovarian cancer include age, infertility, nulligravidity, endometriosis, hereditary ovarian cancer, tobacco and asbestos.

Protective factors for ovarian cancer include oral contraceptives, bilateral tubal ligation, salpingo-oophorectomy, hysterectomy, and breast feeding [76]. It is a difficult cancer to diagnose early, with approximately 60% of the individuals diagnosed after the cancer has metastasized from the pelvic region, where this cancer begins. In the meta-analysis, comparing ovarian cancer risk among women who used talc versus those who

never used talc (using both case-control and cohort designs), we observed an approximate 30% increase in ovarian cancer risk in the group who used talc. The most common type of ovarian cancer seen in the general population, and among the women exposed to talc were of epithelial origin, most common histologic type (accounting for about 95% of all cases in the general population), and of serous morphology, the most common subtype (comprising about 75% in the general population).

The cell-type of origin and morphology of talc induced ovarian cancer is similar to that observed in typical ovarian cancer with approximately 95% derived from epithelium (from fallopian tube fimbriae, ovarian or peritoneal) with serous tumors as the most common subtype. Like most ovarian cancers, those associated with talc exposure are typically diagnosed late in the course of the disease (~60% are diagnosed after the disease has spread outside of the pelvis). This late diagnosis complicates our understanding of the history and origin of the disease.

Demographic factors were analyzed using subgroup analysis where possible, and these were generally consistent with what has been previously observed with respect to ethnicity and risk of ovarian cancer. Additionally, these data also provide support for a mechanism of ovarian cancer induction working via an inflammatory pathway associated with oxidative stress [27, 77, 78].

A small number of studies explored the issue of ethnicity: Asians (1 study), Hispanics (2 studies), and African-Americans and Whites (3 studies each). Among these studies the risk for talc associated ovarian cancer was 1.70 (Hispanics), 1.67 (African Americans), 1.28 (Whites) and 0.04 (Asians). These risk factors compare with the demographics of ovarian cancer in the US population with an overall prevalence of

ovarian cancer of 12.7/100,000 among Whites 13.4/100,00, Hispanics 11.3/100,000, African Americans 9.8/100,000, and Asians 9.8/100,000. The difference in US prevalence and risk of talc induced ovarian cancer among Hispanics and African Americans may provide further evidence concerning exposures or mechanism of action [76].

A variety of factors were assessed with respect to the studies contributing to the meta-analysis, including study quality (NOS) and publication year. In general, the risk of talc associated ovarian cancer was similar among studies with an NOS ≥ 7 or NOS < 7 . Year of publication also failed to demonstrate a significant impact on reported talc risk estimates.

4.2. Exposure metrics

Given that the epidemiological studies indicate that talc is a possible human carcinogen, we next evaluated the studies to identify those comparing differences in exposure. The initial assessment exploring frequency of use, utilized a qualitative exposure metric: low, medium and high. Ovarian cancer was observed to increase between the medium and high exposure groups, consistent with an exposure-response relationship. Several studies explored duration of use (years) and risk of ovarian cancer; 20+ years (2 studies), 10 (5 studies), 10/20 (2 studies), and observed that the risk was greatest in the 20+ year exposure group, followed by lower risk in the 10/20 year and <10-year exposure groups.

Several studies explored the route of exposure or approach to talc application on ovarian cancer risk, including; hysterectomy, bilateral tubal ligation, diaphragm,

underwear, sanitary napkin, as these can provide insight into differences in exposure of the fallopian tube, ovarian and peritoneal epithelium. Use of a diaphragm, as well as tubal ligation act to interrupt exposure of perineal talc to reproductive tract. In contrast, application to underwear and sanitary napkin exposure will provide broader exposures. As hypothesized, the use of diaphragm and bilateral tubal ligation decreased ovarian cancer risk [22].

4.3. Modifying Factors

Modifiers of the risk of ovarian cancer, either associated with talc exposure, or a spontaneous disease, can provide clues to potential mechanisms of causation. Menopausal status and use of hormones can modify the risk for ovarian cancer. For example, among post-menopausal women receiving hormonal therapy the risk for ovarian cancer is greater than those who are premenopausal and those who are post-menopausal not receiving hormone therapy. It has also been observed that women receiving fertility treatment who do not become pregnant are at greater risk for ovarian cancer [22]. These data suggest that hormonal status (elevated estrogens and/or gonadotropins) plays a role in the mechanism of action of talc associated ovarian cancer.

Subgroup analyses in the meta-analysis indicated that interruption of the pathway from perineum to pelvis (as with bilateral tubal ligation or use of diaphragm) decreased risk for ovarian cancer. This supports the hypothesis that talc acts by local action on the ovary. Given the data developed in non-human studies suggesting an inflammatory response of epithelial cells to talc, and histological observations

corroborating those observations, additional support for an inflammatory pathway leading to ovarian cancer is provided. One study recently explored the use of anti-inflammatory drugs and observed a decreased risk for ovarian cancer, also supporting the importance of an inflammatory pathway with oxidative stress [77].

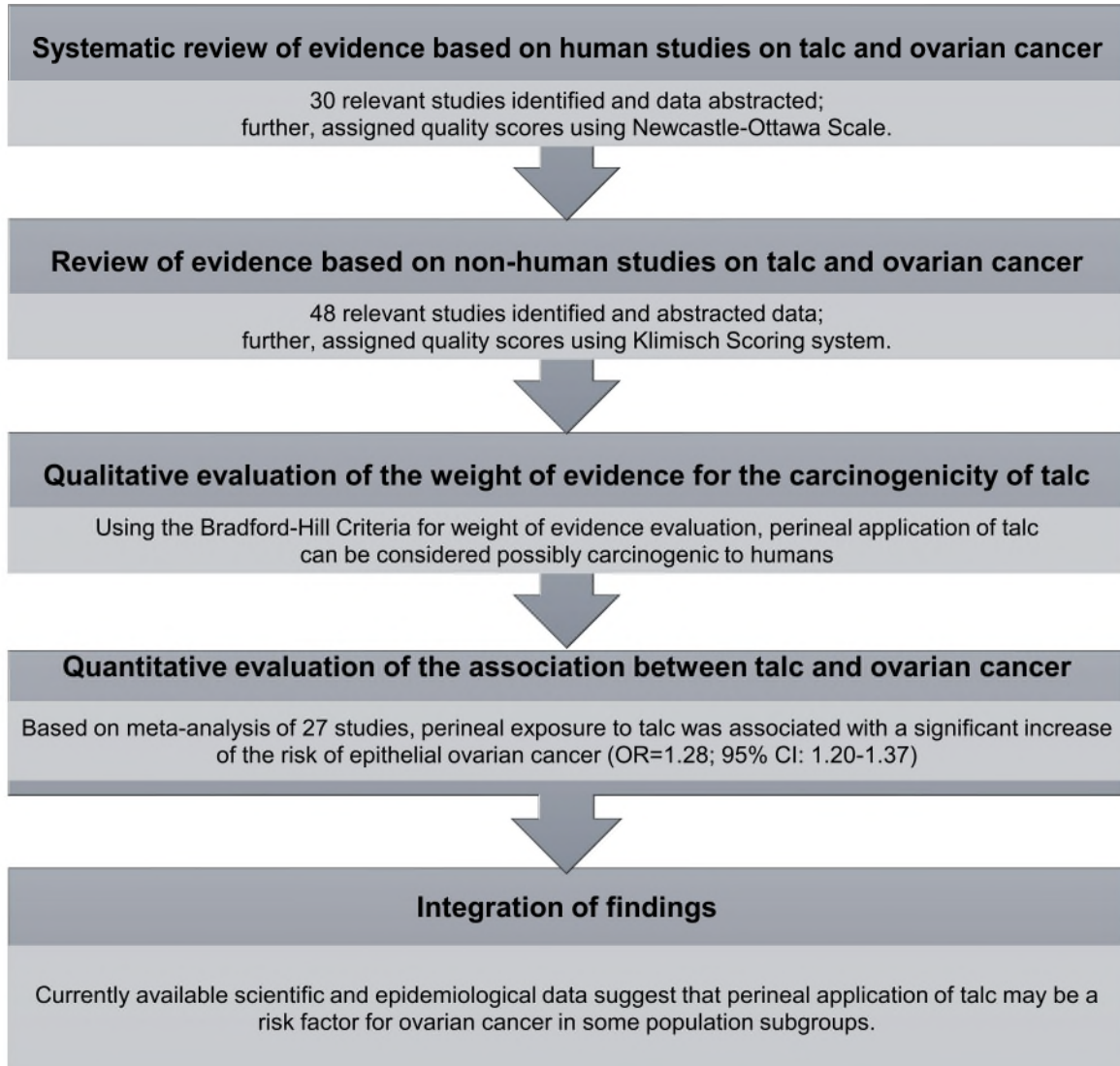


Figure 4: Detailed process flow for assessment of talc carcinogenicity

5. Conclusion

We conducted an extensive search, examination, assessment and analysis of evidence from published human and non-human original as well as all published reviews that considered the association between genital/perineal use of talc powder and risk of ovarian cancer. The steps followed in conducting this review are summarized in Figure 4, along with the key findings at each step. Consistent with previous evaluations the IARC in 2010 [2], and subsequent evaluations by individual investigators [3, 5, 69], the present comprehensive evaluation of all currently available relevant data indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans.

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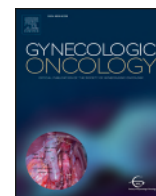
Exhibit 58



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Talc and ovarian cancer

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HIGHLIGHTS

- Talc use has been linked to the risk of ovarian cancer in many case-control studies.
- Genital talc use is much less common now than it was in earlier cohorts of women in North America.
- It is not possible to say that any specific case of ovarian cancer was the result of talc use.

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Interest in a possible link between talcum powder and ovarian cancer risk dates back to the 1960s when the public was concerned about asbestos contamination in talc. Talc has been in the news intermittently since then, but the story of talc and ovarian cancer made the front page in February 2016, when the family of an ovarian cancer patient successfully sued Johnson and Johnson for 72 million dollars. This surprising jury decision raises a few questions. Is there a real and robust statistical association between talc use and ovarian cancer, and if so, is the association causal or due to confounding? What is the risk of cancer associated with talc use and how do we tell if a particular case of ovarian cancer was caused by talc? What should we tell our patients?

Most of the evidence comes from case-control studies. In 2013, the Ovarian Cancer Association Consortium pooled eight of these and analysed 8525 cases and 9859 controls [1]. They reported that genital powder use was associated with a modest but significant increased risk of epithelial ovarian cancer (OR = 1.24; 95% CI 1.15–1.33). The association between talc and ovarian cancer was significant in five of the eight individual studies. More recently, Cramer et al. studied 2041 cases and 2100 controls (some of whom were included in the OCAC study) [2]. They

estimated the risk of ovarian cancer associated with genital talc use to be 1.33 (95% CI 1.16 to 1.52). The case-control studies to date are consistent; given the small effect size it is not surprising that some are positive (i.e., show a significant increase in risk) and some are negative (i.e., show a non-significant increase in risk or no risk difference). Some say, based on this data, that there is little or no evidence that talc is associated with ovarian cancer. This is a conservative opinion, based on an uncompromising interpretation of statistics and a demand for proof. For the sake of argument, let us suppose that the true risk ratio for ever use of talc and the development of ovarian cancer is 1.2. This estimate is the one generated from the large pooling study [1] and is the level of risk that is under discussion in the media. It is possible that the true risk might be lower or higher than this single estimate. In this scenario, where talc increases the risk of ovarian cancer by 20% beyond the baseline of 1.3% lifetime, it would be challenging to convince the epidemiology community that there is a danger. Simply put, a risk ratio of this size falls outside the resolution of most epidemiologic studies; for example, if we set the *p*-value for significance at 0.05, then, in order to have a power of 0.80 to discriminate an increase in risk of 20%, and if 20% of the population is exposed to talc, we would require a case-control study of 2801 cases and 2801 controls. This is a very large sample for a case-control study, especially given that ovarian cancer is rare and only but the large study of Cramer et al. the pooled analyses of OCAC were designed to detect and odds ratios this small [1,2]. If the

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magnitude of the association is to be estimated with precision it is important that consortia are developed and expanded in order to generate the appropriate sample size.

Prospective observational studies are less prone to bias than case-control studies, and for this reason they are given greater weight. In particular, they are not prone to recall bias (where the accuracy of the recollection of the exposure differs between cases and controls); selection bias (where the unexposed and exposed women are not equally likely to be ascertained for study) and survivorship bias (which would occur if the survival of women with ovarian cancer differs, depending on prior talc exposure). In the Nurses Health Study, 78,630 women were followed for a mean of 12.9 years [3]. There were 307 ovarian cancers diagnosed in the follow-up period. There was no overall association with ever-use of talc (HR = 1.09; 95% CI 0.86 to 1.37, but there was a modest and significant increased risk for serous ovarian cancer (HR = 1.40; 95% CI: 1.02–1.91). These figures could be dismissed as non-significant or as due to chance, but if the real risk were in fact 1.2, this is about what we would expect. In the Women's Health Initiative [4], 61,285 women were followed for an average of 12.4 years. 53% of the women reported perineal talc use (a very high proportion). The adjusted hazard ratio for serous ovarian cancer was 1.13, but this was not significant (95% CI 0.84 to 1.51). Neither prospective study confirmed the association of talc use and ovarian cancer raised by the case-control studies, but neither study was powered to detect a risk of 1.2 and therefore we cannot exclude the possibility. Only two women in a thousand will develop ovarian cancer in a ten-year follow-up period. If we study 10,000 women over 10 years we can expect 20 cancers to occur. If the true odds ratio is 1.2, we will expect 20 cancers in an unexposed group of 10,000 women and 24 cancers in an exposed group of equal size and this difference will not be significant ($p = 0.65$). In order to achieve statistical significance in a prospective study, we need a much larger cohort, e.g., we will need to study upwards of 200,000 women for ten years.

Given this inherent limitation of cohort studies, it is not surprising that we have not been able to confirm the case-control studies with prospective studies, but this does not mean that the case-control studies were wrong. I don't think it is because the prospective studies are free from the biases that plague the case-control studies (e.g., recall bias) — I think the parsimonious explanation is that they lack statistical power. It is well that we also consider various possible biases as a source of imprecision in case-control studies. In the case of talc and ovarian cancer we should consider recall bias, survivorship bias and confounding bias. The idea behind recall bias is that a case is more likely to (correctly) recall the past use of talc than a control (who might forget) or that a case is more likely than a control to (incorrectly) report the use of talc that was never used. In studies where simple exposures that are coded as never/ever use recall bias unlikely to be an important source of bias. Survivorship bias would occur if we used prevalent cases and the use of talc was associated with better or worse survival, once ovarian cancer develops. There is no reason to assume that this is the case.

Confounding bias may be more subtle. When people say that 'association is not causality' they mean to say that that talc may not actually cause ovarian cancer but both talc and ovarian cancer may be linked to a third factor such as birth control pills — perhaps women who use talc are less likely to use birth control pills and therefore form a high risk group. Hardly likely — and the other risk factors for ovarian cancer are parity, breast feeding and tubal ligation. None of these are a priori likely to be confounders and in any case, most case-control studies will adjust for these. The most important potential confounder is year of birth (see below) and it is critical to control for this. It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer it is likely to be causal (albeit with intermediate factors such as inflammation). In any case, given the number of hazard ratios reported in the literature between 1.1 of 1.4 in both case-control and cohort studies, it is disingenuous to state that there is no evidence that talc is associated with ovarian cancer.

It has been suggested that talc passes through the cervix and endometrium and becomes lodged in the fallopian tube where it induces an inflammatory reaction [5]. This is hypothetical, but is supported by the observation of talc particles within the pelvic organs [6] and fits with the paradigm that most serous ovarian cancers originate in the fallopian tube and that intra-epithelial lesions in the fallopian epithelium are the earliest manifestations of an impending ovarian cancer [7]. If the model is correct, it is possible that the passage of talc is aided by retrograde menses and that talc use during menses poses a special risk. This might explain in part why the association between talc applied to sanitary napkins and ovarian cancer is among the most consistent. Against the model is the observation that, in the prospective studies, the relative risk of cancer associated with talc was not lower in women who had a tubal ligation [3,4] (and presumably had blocked access to talc).

If we accept that the actual hazard ratio for ever-use versus never-use is 1.2 how are we to interpret this number? If we consider a particular woman who uses talc regularly, her lifetime risk of ovarian cancer would increase from about 1.3% to 1.6%, an increase of 0.3% or three cases in a thousand. On a yearly scale, the risk rises from 20 per 100,000 women per year to 24 per 100,000 per year or four cancer cases for every 100,000 talc users. The latter might strike as more favorable, but, in fact describes the same risk. If we consider the population as a whole, the total number of ovarian cancer cases caused by talc depends on the frequency of talc use in the population. It is right to be concerned over the carcinogenicity of talc even if the risk ratio is low, because up to 50% of women are exposed [1]. If 40% of women use talc and the relative risk is 1.2, then 7% of ovarian cancer cases would be attributable to talc use or 1577 cases a year in the USA. This is not a trivial number and should not be dismissed. If 20% of women were talc users the number of cases per year would be 819. If only 5% of women use talc then the number of cases per year would be 211. Few perhaps, but if ovarian cancer is avoidable, it is best avoided. Is there a downside? Talc affords comfort and was used commonly in the past to control moisture and odor but women have many more choices nowadays. One could of course make a recommendation here not to use talc on sanitary napkins, but this will have little impact because few women continue to use it. In our database of 6000 women from North America that we follow at Women's College Hospital, the use of talc on sanitary napkins has declined precipitously from one generation to the next; talc use was recorded by 11% for women born from 1920 to 1940, but for only 1% of women born after 1975. Similarly, the use of talc applied directly to the genital area fell from 19% to 3% over the same period.

In the interests of public health, I believe we should caution women against using genital talcum powder. However, this policy of talc avoidance is unlikely to have much impact nowadays given this downward trend in usage. I don't think we should try to ascribe any particular case of ovarian cancer to prior talc use. The estimate of a risk ratio of 1.2 provides information about the potential contribution of talc to the burden of ovarian cancer in the population, but is not helpful in determining if a specific case is, or is not, the result of talc exposure. Are we able to make helpful recommendations for women who have used it in the past but who no longer use it? Probably not, we do not offer preventive surgery for women with a risk of ovarian cancer that is less than 2% and screening with CA125 or ultrasound is not recommended to women at average or slightly increased risk.

Conflict of interest

The author declares no conflict of interest.

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Exhibit 59

Draft Screening Assessment

Talc
(Mg₃H₂(SiO₃)₄)

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of talc. The Chemical Abstracts Service Registry Number (CAS RN¹) for talc is 14807-96-6. This substance is among those substances identified as priorities for assessment as it met categorization criteria under subsection 73(1) of CEPA.

Talc is a naturally occurring mineral. According to information reported under section 71 of CEPA and publically available information, in 2011 talc was manufactured in Canada in quantities ranging between 50 to 75 million kg, and in 2016, approximately 100 million kg of talc was imported. In Canada talc is used in adhesives and sealants; automotive, aircraft, and transportation applications; building and construction materials; ceramics; electrical and electronics; textiles; floor coverings; ink, toner, and colourants; lubricants and greases; oil and natural gas extraction applications; paints and coatings; paper and paper products, mixtures, and manufactured items; plastic and rubber materials; toys, playground, and sporting equipment; and in water treatment. The major uses in Canada align with major global uses of talc. Talc is an ingredient in self-care products and is a permitted food additive. In North America, approximately 3 to 4 % of the talc produced and sold is used in cosmetics. High-purity talc is used in cosmetics, while lower-grade talc is used in commercial applications.

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) approach. The ERC-I is a risk-based approach that employs multiple metrics, considering both hazard and exposure in a weight of evidence. Hazard characterization in ERC-I included a survey of past predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of new PNEC values when required. Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model for each substance, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. Modelled and measured predicted environment concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment. The ERC-I identified talc as having a low potential to cause ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is a low risk of harm to the environment from talc. It is proposed to conclude that talc does not meet the criteria under paragraphs 64(a) or (b) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that have or

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may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Talc has been reviewed internationally by other organizations, including the International Agency for Research on Cancer (IARC) and the Danish Environmental Protection Agency. These assessments informed the human health risk assessment.

No critical health effects were identified via the oral or dermal routes of exposure. As such, oral exposure to talc resulting from food intake and self-care products is not of concern. Inhalation exposure from industrial and commercial uses of talc was not identified to be of concern for human health given the limited number of sites producing and processing talc in Canada. Rather, the focus of the assessment is on inhalation and perineal exposure to certain self-care products containing cosmetic- or pharmaceutical-grade talc.

With respect to inhalation exposure, non-cancer lung effects were identified as a critical health effect for risk characterization on the basis of United States National Toxicology Program studies conducted with rats and mice exposed to cosmetic-grade talc. There is potential for inhalation exposure to talc powder during the use of certain self-care products (e.g., cosmetics, natural health products, non-prescription drugs formulated as loose powders). Self-care products formulated as pressed powders (e.g., face makeup) are not of concern. Margins of exposure between air concentrations following the use of dry hair shampoo and critical lung effects observed in animal studies are considered adequate to address uncertainties in the health effects and exposure databases. Margins of exposure between air concentrations following the use of loose powders (e.g., body powder, baby powder, face powder, foot powder) and critical lung effect levels observed in animal studies are considered potentially inadequate to address uncertainties in the health effects and exposure databases.

The meta-analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. Further, available data are indicative of a causal effect. Given that there is potential for perineal exposure to talc from the use of various self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs), a potential concern for human health has been identified.

Based on the available information, it is proposed that there is potential for harm to human health in Canada at current levels of exposure. Therefore, on the basis of the information presented in this draft screening assessment, it is proposed to conclude that talc meets the criteria under paragraph 64(c) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that talc meets one of the criteria set out in section 64 of CEPA.

Talc is proposed to meet the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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1. Introduction

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of talc to determine whether this substance presents or may present a risk to the environment or to human health. This substance was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2017]).

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) approach (ECCC 2018). The ERC-I is a risk-based approach that employs multiple metrics, considering both hazard and exposure in a weight of evidence. Hazard characterization in ERC-I included a survey of past predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of a new PNEC value when required. Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model for each substance, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. Modelled and measured predicted environmental concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment.

With respect to human health, this draft screening assessment includes the consideration of information on chemical properties, environmental fate, hazards, uses, and exposures, including additional information submitted by stakeholders. Relevant data were identified up to August 2018. Empirical data from key studies, as well as results from models, were used to reach proposed conclusions. Talc has been reviewed internationally through the International Agency for Research on Cancer (IARC) Monographs Programme, United States Environmental Protection Agency (U.S. EPA), the Joint Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and the Danish Environmental Protection Agency (Danish EPA). Talc was also assessed by the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) in Germany and the Cosmetic Ingredient Review (CIR) Expert Panel. These evaluations and reviews were used to inform the health effects characterization in this screening assessment. This assessment focuses on health effects associated with cosmetic-grade talc and not on potential impurities, such as asbestos. Engineered nanomaterials composed of or containing talc are not explicitly considered in this assessment.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and the Consumer Product Safety Directorate at Health Canada and incorporates input from other programs within these departments. The ecological portion of the assessment is based on the ERC-I document (published May 11, 2018), which was subject to an external peer review and a 60-day public comment period. The human health portion of

this assessment has undergone external peer review and/or consultation. Comments on the technical portions relevant to human health were received from Ms. Lopez, Ms. Super, and Ms. Jeney of Tetra Tech. Although external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution.² This draft screening assessment presents the critical information and considerations on which the proposed conclusion is based.

2. Identity of substance

Talc (CAS RN³ 14807-96-6) is one of the softest naturally occurring minerals, made up of magnesium, silicon, and oxygen (ChemIDplus 1993-). The term talc refers to both the pure mineral and a wide variety of soft, talc-containing rocks that are mined and used for a variety of applications (Kogel et al. 2006). Relatively pure talc ore is also referred to as steatite, and soapstone refers to impure, massive talc rock (Fiume et al. 2015).

The mineral talc is composed of triple-sheet crystalline units, consisting of two silicate sheets composed of SiO₄ tetrahedra joined by edge-link MgO₄(OH)₂ (Zazenski et al. 1995). These layers, held together loosely via van der Waals forces, slide over one another easily, giving talc its slippery feel and accounting for its softness (Fiume et al. 2015). The size of an individual talc platelet (i.e., a few thousand elementary sheets) can vary from approximately 1 µm to over 100 µm, depending on the conditions of formation of the deposit (Eurotalc 2017). The individual platelet size determines the lamellarity of a sample of talc. Highly lamellar talc will have large individual platelets, whereas microcrystalline talc will have small platelets. Other inorganics in place of magnesium and silicon are common in talc; for example, aluminum and iron may substitute for silicon in the tetrahedral sites, or manganese may substitute for magnesium in the octahedral positions (Zazenski et al. 1995).

² A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion on the basis of the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

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Commercially exploited talc contains 20 to 99 % of the pure mineral (Kogel et al. 2006). Some of the most common minerals that occur with talc are carbonates (e.g., dolomite, calcite, magnesite) and chlorite (i.e., magnesium aluminum silicate) (CIR 2013). Less common minerals include quartz, mica, iron oxides, pyrite, serpentine, and amphibole. Selective mining, ore processing, and beneficiation can remove many of the impurities (Kogel et al. 2006). There is a trend towards upgrading and higher-purity talc; however, many applications require the properties of the minerals associated with talc (Kogel et al. 2006). The purity of the source talc will influence its uses.

There are different grades of talc that refer to the purity (presence of other minerals). Pharmaceutical-grade talc conforms to the United States Pharmacopeia (USP) specifications (or similar specifications); these specifications require the absence of asbestos and set limits on iron, lead, calcium, and aluminum (USP 2011). As per B.01.045 of the *Food and Drug Regulations*, when used as a food additive talc must comply with Food Chemical Codex specifications or the Combined Compendium of Food Additive Specifications, prepared by the Joint FAO/WHO Expert Committee on Food Additives, and must be free from asbestos (FAO 2006).

Cosmetic-grade talc should comply with USP standards that require a limit of 20 ppm lead and an absence of asbestos (Fiume et al. 2015). Historically, some talc source materials were contaminated with asbestos; however, in 1976 the Cosmetic Toiletry Fragrance Association (CTFA) set purity standards for cosmetic-grade talc (Fiume et al. 2015). In Canada, the *Prohibition of Asbestos and Products Containing Asbestos Regulations* to be made under CEPA 1999 will prohibit asbestos above trace levels in consumer products, including cosmetics. Health effect studies on cosmetic-grade talc cited in this assessment were considered to be free of asbestos.

Talc is milled to different particle sizes for specific commercial applications. Most talc for cosmetics and pharmaceuticals are pure 200-mesh roller-milled talc (Kogel et al. 2006). In 200-mesh talc (preferred for body powder and deodorants), the particle size distribution allows 95 to 99 % of the product to pass through a 200-mesh (74 µm) screen (Zazenski et al. 1995; Kogel et al. 2006). The finer 325-mesh talc is also used in cosmetic-, pharmaceutical-, and food-grade formulations, where 95 to 99 % of the product passes through a 325-mesh (44 µm) screen.

3. Physical and chemical properties

A summary of physical and chemical properties of talc is presented in

Table 3-1. Talc is hydrophobic and lipophilic (Kogel et al. 2006).

Table 3-1. Experimental physical and chemical property values (at standard temperature) for talc

Property	Range	Key reference
Physical state	solid, powder	HSDB 2005
Melting point (°C)	1500	Eurotalc 2017
Vapour pressure (mm Hg)	approx. 0, negligible at 20°C	OSHA 1999; NIOSH 2014
Water solubility (mg/L)	insoluble	HSDB 2005
Specific gravity (unitless)	2.58–3.83	HSDB 2005

4. Sources and Uses

Talc is a naturally occurring mineral, and there are deposits of talc in most provinces of Canada (Kogel et al. 2006). Currently, there is one producing mine (open-pit) and concentrator facility in Canada, in Penhorwood Township near Timmins, Ontario, and one micronizing facility in Timmins (Kogel et al. 2006; MAC 2016; NPRI 2018). The talc ore from the mine is approximately 45 % pure, with magnesite, magnetite, chlorite, and serpentine as the major impurities (Kogel et al. 2006). After beneficiation, this mine and micronizing facility produces talc primarily for the paper, plastics, paint, and ceramic sectors (Kogel et al. 2006). In 2017, China was the largest producer of talc, followed by India, Brazil, Mexico, and Korea (USGS 2018). The major uses of talc globally include paper, plastics, paint, ceramics, putties, and cosmetics (USGS 2000; Kogel et al. 2006; EuroTalc 2017; USGS 2018) and are aligned with Canadian uses.

On the basis of information submitted pursuant to a CEPA section 71 survey for the year 2011, talc was reported to be manufactured and imported in Canada at quantities ranging from 50 to 75 million kg (EC 2013).⁴ According to the Canadian International Merchandise Trade (CIMT) database, in 2016, 99 549 000 kg of natural steatite and talc, crushed or powdered (Harmonized System, HS code 252620) and 4 656 000 kg of natural steatite and talc, not crushed, not powdered (HS code 252610) were imported into Canada (CIMT 2017).

According to information reported pursuant to a CEPA section 71 survey, results from voluntary stakeholder engagement (ECCC, HC 2017), and a search of websites from talc producers, manufactured or imported talc is used in Canada in: adhesives and sealants; automotive, aircraft, and transportation applications; building and construction materials (e.g., wood and engineered wood); ceramics; electrical and electronics; textiles; floor coverings; ink, toner, and colourants; lubricants and greases; oil and natural gas extraction applications; paints and coatings; paper and paper products,

⁴ Values reflect quantities reported in response to the survey conducted under section 71 of CEPA (EC 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

mixtures, or manufactured items; plastic and rubber materials; toys, playground, and sporting equipment; and in water treatment.

Talc is a formulant in pest control products registered in Canada (Health Canada 2010, Personal communication, email from the Pest Management Regulatory Agency, Health Canada to the Risk Management Bureau, Health Canada, dated March 29, 2017; unreferenced).

Additionally, in Canada talc is on the List of Permitted Food Additives with Other Accepted Uses for limited uses in a small number of foods (Health Canada [modified 2017]). Talc can be used as a coating agent on dried legumes and rice and as a filler and dusting powder for chewing gum as per the List of Permitted Food Additives with Other Accepted Uses, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. It may be present in food packaging materials and in incidental additives⁵ used in food processing establishments (email from the Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated March 31, 2017; unreferenced).

Talc is present in approximately 8500 self-care products.⁶ Talc is marketed or approved as a non-medicinal ingredient in approximately 1600 human and veterinary drug products in Canada, including approximately 150 over-the-counter (OTC) or non-prescription products (email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017; unreferenced). Talc is listed in the Natural Health Products Ingredients Database (NHPID [modified 2018]) with a medicinal role and classified as a natural health product (NHP) substance falling under item 7 (a mineral) of Schedule 1 to the *Natural Health Products Regulations* and with a non-medicinal role (NHPID [modified 2018]). Talc is listed in the Licensed Natural Health Products Database (LNHPD) as being present as a medicinal or non-medicinal ingredient, in currently licensed natural health products in Canada (LNHPD [modified 2018]). Talc is present as a medicinal or a non-medicinal ingredient in approximately 2000 active licensed NHPs. Talc is listed as a medicinal ingredient in diaper rash products in concentrations ranging from 45 to 100 % in the Diaper Rash Monograph (Heath Canada 2007); however, there are no diaper rash products listed in the LNHPD containing talc as a medicinal ingredient (LNHPD [modified 2018]). Talc is permitted as a medicinal ingredient in the monograph for Traditional Chinese Medicine Ingredients (Health Canada 2015).

⁵ While not defined under the Food and Drugs Act (FDA), incidental additives may be regarded, for administrative purposes, as those substances that are used in food processing plants and that may potentially become adventitious residues in foods (e.g., cleaners, sanitizers).

⁶ Self-care products are products available for purchase without a prescription from a doctor, and fall into one of three broad categories: cosmetics, natural health products, and non-prescription drugs.

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, talc is an ingredient in approximately 6500 cosmetic products in Canada (dated April 5, 2017, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Talc is considered a restricted ingredient in cosmetics.⁷ The Cosmetic Ingredient Hotlist entry for cosmetics containing talc in powder form intended to be used on infants and children indicates that product labels should display text to the effect of “keep out of the reach of children” and “keep powder away from child’s face to avoid inhalation that can cause breathing problems.” High-purity talc (fewer impurities of other minerals) is used in cosmetics, while lower-grade talc is used in the many commercial applications mentioned above. In North America, approximately 3 to 4 % of the talc produced and sold is used in cosmetics (Kogel et al. 2006; USGS 2018).

Condoms and medical gloves are regulated as Class II medical devices in Canada under the *Medical Devices Regulations* and may be sources of exposure if talc is present as a dry lubricant. However, a 1998 study did not find talc in a small survey of condoms tested in Canada (Douglas et al. 1998). Condom standards require dry lubricants to be bioabsorbable, such as starch and calcium carbonate (WHO, UNFPA, FHI 2013). Starch is more commonly used as dry powder lubricant on condoms (Douglas et al. 1998). There was also a shift from the use of talc as a dry lubricant on medical patient examination gloves to cornstarch in the 1980s (Lundberg et al. 1997). In 2016, the U.S. Food and Drug Administration banned powdered patient examination gloves (United States 2016).

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I). The ERC-I is a risk-based approach that employs multiple metrics that consider both hazard and exposure in a weight of evidence. Hazard characterization in ERC-I included a survey of past domestic and international assessment PNECs and water quality guidelines. When no suitable existing PNEC or water quality guideline was found, hazard endpoint data were collected and, dependent on data availability, either a species sensitivity distribution (SSD) or an assessment factor (AF) approach was taken to derive a new PNEC value. In the case of talc, hazard endpoint data from the Organisation for Economic Co-operation and Development

⁷ Talc is described as a restricted ingredient on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances may contravene the general prohibition found in section 16 of the *Food and Drugs Act* (FDA), or may contravene one or more provisions of the *Cosmetic Regulations*. Section 16 of the FDA states that “no person shall sell any cosmetic that has in or on it any substance that may cause injury to the health of the user.” In addition, the Hotlist includes certain substances that may make it unlikely for a product to be classified as a cosmetic under the FDA (Health Canada [modified 2018]).

Screening Information Dataset (SIDS) for synthetic amorphous silicates (OECD 2004) were identified for read across (ECCC, HC 2017) and an AF approach was used to derive a PNEC value of 40 mg/L.

Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. The generic near-field exposure model used input data, when available, from the National Pollutant Release Inventory (NPRI), the DSL–Inventory Update (DSL-IU), international trade data from the Canada Border Services Agency (CBSA), and third-party market research reports to generate PECs. In the case of talc, input data from the DSL-IU and CBSA were available.

Modelled PECs were compared to PNECs, and statistical metrics considering both the frequency and magnitude of exceedances were computed and compared to decision criteria to classify the potential for ecological risk as presented in ECCC (2018). The results are summarized in Table 5-1. The ERC-I identified talc as being of low ecological concern.

Table 5-1. Ecological risk classification of inorganics results for talc

Monitoring (total/extractable)	Monitoring (dissolved)	Modelling (DSL-IU)	Modelling (NPRI)	Modelling (CBSA)	Overall ERC-I score
NA	NA	Low	NA	Low	Low

Abbreviations: NA, Not Available.

6. Potential to cause harm to human health

6.1 Health effects assessment

Talc was previously reviewed internationally by the IARC, and an IARC monograph is available (IARC 2010). Additionally, talc was reviewed by the United States Environmental Protection Agency (U.S. EPA), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) in Germany, and the Danish Environmental Protection Agency (Danish EPA) (U.S. EPA 1992; JECFA 2006; MAK-Commission 2012; Danish EPA 2016). Talc's safety in cosmetic uses was also assessed by the CIR Expert Panel (CIR 2013; Fiume et al. 2015).

A literature search was conducted from the year prior to the most recent assessment (the 2016 Danish EPA review), i.e., from January 2015 to January 2018. No health effects studies that could impact the non-cancer risk characterization (i.e., result in different critical endpoints or lower points of departure than those stated in existing reviews and assessments) for oral, dermal, or inhalation exposures were identified. For perineal exposures, recently published literature was identified and considered in the assessment.

The health effects of talc are outlined by route of exposure in the following sections.

Toxicokinetics

Talc is poorly absorbed via the oral route of exposure. Following gavage administration of radiolabelled talc to rodents, the majority of the administered dose (AD) remained in the gastrointestinal (GI) tract and was eliminated and recovered in the faeces ($\geq 95.8\%$ of AD) within three to four days of dosing (Wehner et al. 1977a; Phillips et al. 1978). Less than 2 % of the AD was recovered in the urine; however, this was mainly attributed to contamination from faeces during collection, with true absorption and urinary clearance expected to be even lower. At 24 hours post administration, less than 2 % of the AD remained in the carcass of hamsters; no radioactivity was detected in mouse carcasses at this time point. In rats and guinea pigs, only trace amounts of radioactivity remained in the GI tract at 10 days post administration.

As an insoluble solid, talc is not expected to be absorbed when applied to healthy and intact skin. There are no indications of dermal absorption following talc exposure (MAK-Commission 2012).

Inhalable talc particles ($<10\ \mu\text{m}$) are eliminated from the respiratory tract via mucociliary clearance. In female Syrian hamsters that were administered aerosolized neutron-activated cosmetic talc at concentrations of 40 to 75 mg/m³ (95% pure; MMAD 6.4 to 6.9 μm) over a 2-hour exposure period, 6 to 8 % of the AD was deposited into the alveoli (Wehner et al. 1977b). The biological half-life following a single exposure was estimated to be between 7 and 10 days, with complete alveolar clearance after 4 months. There was no translocation of talc from the respiratory tract to the liver, kidneys, ovaries, or other parts of the body. Lung clearance was noted to be longer in other species. The Danish EPA (2016) noted that talc, including the respirable fraction ($< 4\ \mu\text{m}$), is not absorbed following inhalation, but is retained in the lung tissue. They further stated that lung burdens were proportional to respired concentrations, and clearance became impaired with increasing exposures. Pulmonary retention half-lives for talc particles in the lungs of rats from a chronic inhalation study were estimated to be as long as 300 days (Oberdorster 1995). Other authors (Pickrell 1989; MAK-Commission 2012) noted similar findings indicating that with repeat exposures, alveolar clearance in rats may be impaired at concentrations of only 2 mg talc/m³ air.

Talc particles have been observed and detected in the ovaries of humans (Heller et al. 1996a, 1996b), and perineal exposure to talc has also been associated with a presence of talc in lymph nodes and ovaries of women diagnosed with ovarian cancer (Heller et al. 1996b; Cramer et al. 2007). Migration of talc particles from the vagina to the ovaries has been identified as a plausible explanation of these findings (Henderson et al., 1986), and retrograde movement of talc particles in humans through the reproductive tract to the ovaries has been suggested (Heller et al. 1996b; Cramer et al. 2007). Inert particles with the same size as talc (5 to 40 μm in diameter) and placed in the vagina can be transported to the upper genital tract (Egli and Newton 1961; De Boer 1972; Venter and Iturralde 1979).

According to a review by the MAK-Commission (2012), there are no indications of metabolism via typical degradation pathways from which toxicologically relevant degradation products may develop.

Health Effects

Oral route of exposure

Talc was considered be of low concern with respect to human health via oral exposure. Repeated-dose testing with talc in animals did not produce any adverse effects via oral exposure with respect to repeated-dose toxicity, carcinogenicity, reproductive/developmental toxicity, or mutagenicity (Gibel et al. 1976; Wagner et al. 1977; NTP 1993; IARC 2010; Danish EPA 2016).

Talc has not been shown to produce adverse effects when ingested orally; as a result, the use of talc in various tablet formulations was not considered hazardous via the ingestion route (Hollinger 1990; U.S. EPA 1992).

In addition, the Commission of the European Communities' report on Dietary Food Additive Intake in the European Union identified talc as having an Acceptable Daily Intake (ADI) of "not-specified." The JECFA has also assessed talc and assigned an ADI as "not specified" due to the lack of toxicity from oral exposure. The substance was considered not to be a hazard to human health at oral intake levels noted in total diet surveys, which represent the majority of the sources of oral exposure for this substance (IARC 1987; EU [modified 2001]). Furthermore, talc is considered as "generally recognized as safe" when used as a food additive in the United States (U.S. FDA GRAS list) without being subject to pre-market approval requirements (U.S. FDA 2015; 2016).

Dermal route of exposure

There are limited data available on repeated-dose studies via dermal exposure to talc (Danish EPA 2016). In the available literature, only one repeated-dose dermal toxicity study was identified (Wadaan 2009). Severe limitations were noted for this study, including a lack of information on the test substance and the dose applied, as well as a lack of detail regarding the test animals. Skin dryness and erosion were noted; however, application sites were shaved, indicating that talc may have been applied to broken skin. As such, the results of this study were not considered appropriate to inform the characterization of health effects via dermal exposure. Additionally, there were no indications of irritation, sensitization, or dermal absorption following exposure to unabraded and/or non-diseased skin (MAK-Commission 2012). A three-day occlusive application of pharmaceutical-grade talc did not show any signs of irritation in 5 human volunteers (Frosch and Kligman 1976, as reported in MAK-Commission 2012).

Case reports, however, do indicate that the application of talc to diseased or broken skin can cause the formation of granulomas, particularly if the talc particles have a large diameter (MAK-Commission 2012; CIR 2013; Fiume et al. 2015). Granulomas have

been observed in the umbilical regions of infants, in the testes, on the vocal cords, in the urinary tract, and during phlebectomies following contact with talc-powdered surgical gloves (Ramlet 1991, Simsek et al. 1992, as reported in MAK-Commission 2012). As a result, the CIR concluded that “talc should not be used on skin where the epidermal barrier is removed or on skin that has greater than first degree burns.”

Although dermal contact with talc is expected from the use of various products available to consumers, talc is a solid powder that is insoluble in water (Table 3-1). As a result, it cannot readily penetrate intact skin, and therefore systemic absorption through the skin is not expected. Consistent with other international regulatory and advisory bodies (Danish EPA, U.S. EPA, MAK-Commission, U.S. FDA, and JECFA), a dermal health effects endpoint has not been identified for talc.

Inhalation route of exposure

Human studies

The Danish EPA (2016) noted that talc is not absorbed via inhalation. Rather, particles are retained in the lung, and lung burdens increase proportionally with exposure concentrations or frequency. The report detailed epidemiological data that noted mortalities in workers due to lung diseases, following exposures to talc. However, it was stated that there was no increase in the lung cancer rate in talc millers in the absence of exposure to carcinogens. A recent meta-analysis by Chang and colleagues (2017) reported a positive association with lung cancer in workers exposed to talc; however, co-exposure to other hazardous materials in the workplace and smoking were not adequately accounted for.

The chronic inhalation of talc leads to lung function disorders and fibrotic changes in humans. Since talc particles are persistent, particles accumulate in human lung tissue. This accumulation may lead to both an impairment of the self-purification function (reduced ability to fight infections) and inflammatory changes and fibrosis. Talc particles may be enclosed in a foreign-body granuloma as the result of an inflammatory reaction. The immobility of the macrophages, which is restricted by the phagocytized talc particles, leads to changes in the function of these cells and subsequently to chronic inflammatory reactions (Gibbs et al. 1992).

In humans, there are reports of pure talc-induced pneumoconiosis or talcosis following inhalation exposure to talc. Talcosis has been reported to occur in miners, millers, rubber workers, and other occupational groups exposed to talc without asbestos or silica (Vallyathan and Craighead 1981; Feigin 1986; Gibbs et al. 1992; Akira et al. 2007). Specifically, a recent longitudinal survey of French and Austrian talc workers found that the prevalence of small radiological opacities and decreases in lung function parameters were related to cumulative exposure. The mean estimated talc dust concentration during the mean duration of follow-up (14.5 years) was 1.46 mg/m³ (Wild et al. 2008). Case reports indicate that patients present with non-specific complaints, including progressive exertional dyspnea, dry or productive cough, with indications of

lung lesions (Marchiori et al. 2010; Frank and Jorge 2011). Talcosis has been shown to occur in children and adults, with symptoms that developed shortly after acute to short-term exposure or up to 10 years later (Patarino et al. 2010; Shakoor et al. 2011). Inhalation of talc has been known to cause pulmonary effects, even following single acute exposures, as reported in a 10-year-old child who had a history of a single exposure to talc at two years of age (Cruthirds et al. 1977). Another case report detailed a seven-year-old child who developed asthma and reduced lung function after a single exposure event (Gould and Barnardo, 1972). Additionally, a 52-year-old woman who used baby talcum powder regularly at least twice a day (usually after bathing for personal hygiene and habitually applying it to her bed sheets nightly) for 20 years was reported to have dyspnea, along with a persistent dry cough and unintentional rapid weight loss. A radiographic exam noted evidence of interstitial lung disease with fibrosis (Frank and Jorge 2011).

Other relevant case reports include the case of a 55-year-old woman, occupationally exposed to talc as a dusting agent on packed rubber balls from 1958 to 1968, who was reported to develop dyspnea during the first five years after exposure (Tukiainen et al. 1984); and a 62-year-old woman occupationally exposed to talc for five years who was reported to have progressive lung fibrosis for more than 40 years (Gysbrechts et al. 1998).

Animal studies

In a repeated-exposure study conducted by the U.S. National Toxicology Program (NTP), groups of F334/N rats were exposed to aerosolized talc via the inhalation route of exposure. Test animals were exposed for 6 hours per day, 5 days per week, for up to 113 weeks (males) or up to 122 weeks (females) to aerosols of 0, 6, or 18 mg/m³ talc (49 or 50 males per group, 50 females per group) (NTP 1993). Mean body weights of rats exposed to 18 mg/m³ talc were slightly lower than those of controls after week 65. No clinical observations were attributed to talc exposure. Absolute and relative lung weights of male and female rats exposed to 18 mg/m³ talc were significantly greater than those of controls. Inhalation exposure produced a spectrum of inflammatory, reparative, and proliferative processes in the lungs. Granulomatous inflammation, which was evident as early as 6 months (first histopathological examination), occurred in nearly all exposed rats, and the severity increased with exposure duration and concentration. Hyperplasia of the alveolar epithelium and interstitial fibrosis occurred in or near the foci of inflammation in many exposed rats, while squamous metaplasia of the alveolar epithelium and squamous cysts were also occasionally seen. Accumulations of macrophages (histiocytes), most containing talc particles, were found in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In exposed male and female rats, there was a concentration-related impairment of respiratory function, beginning at 11 months, which increased in severity with increasing exposure duration. The impairment was characterized by reductions in lung volume (total lung capacity, vital capacity, and forced vital capacity), lung compliance, gas exchange efficiency (carbon monoxide diffusing capacity), and non-uniform intrapulmonary gas distribution (NTP 1993).

In female rats at 18 mg/m³ talc, the incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined) were significantly greater than those of controls (NTP 1993). The incidences of lung neoplasms in exposed male rats were similar to those in controls. Adrenal medulla pheochromocytomas (benign, malignant, or complex [combined]) occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m³ talc groups were significantly greater than those of controls (NTP 1993).

The NTP (1993) concluded that there was some evidence of carcinogenic activity of talc in male rats on the basis of an increased incidence of benign or malignant pheochromocytomas of the adrenal gland. The NTP also concluded that there was clear evidence of carcinogenic activity of talc in female rats on the basis of increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.

In a subsequent symposium, experts from the NTP, along with academic, industry, and government experts re-examined the results of the chronic inhalation studies. The general consensus from the expert panel was that the highest dose tested (18 mg/m³) exceeded the Maximum Tolerated Dose (MTD) and as such, the neoplasms noted were not relevant to human health risk assessment (Carr 1995). A similar conclusion was rendered by Warheit et al. (2016). In addition, the Danish EPA (2016) and the MAK-Commission attributed lung tumours in female rats to the general particle effect of granular biopersistent dusts, which manifests as tumours in rodents only, and not the specific effect of the talc particles. They also attributed the pheochromocytomas to an increase in cell proliferation due to hypoxia, which was considered to be a high-dose effect (MAK-Commission, 2012).

A chronic, repeated-exposure study was conducted in B6C3F1 mice via the inhalation route of exposure (NTP 1993). Test animals were exposed for 6 hours per day, 5 days per week, for up to 104 weeks to aerosols of 0, 6, or 18 mg/m³ talc (47 to 49 males per group, 48 to 50 females per group). Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls. There were no clinical findings attributed to talc exposure. Inhalation exposure of mice to talc at both concentrations was associated with chronic active inflammation and the accumulation of macrophages, which contained talc, in the lung. In contrast to rats, hyperplasia of the alveolar epithelium, squamous metaplasia, or interstitial fibrosis were not associated with the inflammatory response in mice, and the incidences of lung neoplasms in exposed and control groups of mice were similar. Accumulations of macrophages (histiocytes) containing talc particles were also present in the bronchial lymph node. The critical-effect level and corresponding health effects endpoint was a lowest observed adverse effect concentration (LOAEC) of 6 mg/m³ for non-cancer lung effects (NTP 1993).

Doses used in the NTP chronic studies were selected on the basis of the results of a 4-week inhalation study (1993) in which rats and mice were exposed to talc at 0, 2, 6, or 18 mg/m³, 6 hours a day, 5 days a week. Lung burdens were noted to be increased in a

dose-dependent manner, with overload noted by the study authors at 6 and 18 mg/m³ in rats but not at any dose in mice. In both species (mice and rats), a minor macrophage infiltration of lung tissue was the only health effect noted in the high-dose animals, while animals in the mid- and low-dose groups were without treatment-related effects.

In a review of the NTP studies, Oberdorster (1995) revisited the lung deposition data and particle accumulation kinetics in the lungs of rats and mice in those studies, demonstrating that impaired clearance and lung overload was reached at 6 mg/m³ and above, for both sexes, in rats and mice.

A no-observed adverse effect concentration (NOAEC) of 2 mg/m³ was derived from the 4-week study, on the basis of increased lung burden and impaired clearance at a LOAEC of 6 mg/m³ following 4-weeks of dosing, which led to non-cancer lung lesions at this concentration when the duration of dosing was extended. Granulomatous inflammation and alveolar epithelial hyperplasia were noted at a 6 month interim sacrifice in the chronic rat inhalation study, with interstitial fibrosis and impaired lung function noted in some animals at 11 months. As noted previously, following a single exposure in rats, the biological half-life for ciliary clearance was between 7 and 10 days, indicating that previous exposure would not have cleared prior to subsequent exposures, leading to a build-up in lung tissue. A re-examination of the NTP lung burden data by Oberdorster (1995) estimated that lung retention half-lives of talc particles were between 250 and 300 days in the rat chronic study. On the basis of this information, it was considered relevant to combine the NTP studies for the derivation of an appropriate point of departure for lung effects associated with repeated inhalation exposures.

The Danish EPA (2016) used the LOAEC of 6 mg/m³ from the chronic NTP studies (mice and rats) and a NOAEC of 1.5 mg/m³ for talc-induced non-cancer lung effects in the longitudinal survey of French and Austrian talc workers (Wild et al. 2008) to establish a health-based quality criterion for ambient air (QC_{air}) of 0.004 mg/m³.⁸

While human occupational studies and case studies are available, these studies do not provide accurate measures of exposure for use in risk characterization. However, human studies do note a similar range of lung effects and disease as animal models. As such, results from the animal studies noted above were selected for the non-cancer risk characterization. On the basis of the NTP studies with rats and mice exposed to cosmetic-grade talc, a NOAEC of 2 mg/m³ for non-cancer lung effects is considered to be appropriate for the inhalation route of exposure for short- or long-term use (given the long half-life and slow lung clearance of talc from the lungs, even episodic exposures would be expected to increase lung load). The NOAEC of 2 mg/m³ was adjusted according to U.S. EPA guidance on inhalation risk assessment for a comparison with

⁸ The health-based quality criterion in ambient air (QC_{air}) is a reference concentration that refers to the maximum permissible contribution to air from industrial sources.

exposure estimates (U.S. EPA 1994, 2009).⁹ The adjusted NOAEC for non-cancer effects is 0.36 mg/m³.

Perineal exposure to talc

The IARC has classified perineal use of talc-based body powder as “possibly carcinogenic to humans” (Group 2B) on the basis of limited evidence in humans. The analyzed case-control studies found a modest but consistent increase in risk, although bias and confounders could not be ruled out. The IARC Working Group concluded that, taken together, the epidemiological studies provide limited evidence in humans of an association between perineal use of talc-based body powder and an increased risk of ovarian cancer, although a minority of the Working Group considered the evidence inadequate because the exposure-response was inconsistent and the cohort analyzed did not support an association (IARC 2010).

The CIR Expert Panel (2013) determined that there is no causative relationship between cosmetic use of talc in the perineal area and ovarian cancer, and further concluded that talc is safe in the practices of use and concentration described in the CIR safety assessment. Issues noted by the CIR included a lack of consistent statistically significant positive associations across all studies; small risk ratio estimates; a failure to rule out other plausible explanations such as bias, confounders, and exposure misclassifications; and a lack of evidence from studies of occupational exposures and animal bioassays (CIR 2013; Fiume et al. 2015).

Animal studies

Rodents are poor experimental models for perineal studies for a number of reasons. Ovulation in rodents occurs only or mainly during the breeding season, and rodent ovaries are variously enclosed in an ovarian bursa in comparison to human ovaries. Ovarian epithelial tumours are also rare in these animals (Taher et al. 2018). Ovarian tumours do occur in some strains of mice and rats; however, the low incidence and/or the length of time required for the appearance of tumours renders them poorly feasible for experimental studies of ovarian carcinogenesis (Vanderhyden et al. 2003). On account of the limitations detailed above, in addition to the challenges posed by exposing animals via the perineal route, animal data are very limited; one single-dose study and one short-term repeated-dose study were available (Hamilton et al. 1984;

⁹ This adjustment was made according to guidance and equations outlined in the U.S. EPA Supplemental Guidance for Inhalation Risk Assessment (US EPA 2009) and the U.S. EPA Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA 1994). Adjustment of duration to a continuous exposure scenario is done through the use of Equation 1 from U.S. EPA 2009 where the NOAEL[ADJ] = $E \times D \times W$, whereby the NOAEL[ADJ] (mg/m³) = the no-observed adverse effect level (NOAEL) adjusted for the duration of the experimental regimen; E (mg/m³) = the NOAEL or analogous exposure level observed in the experimental study; D (h/h) = the number of hours exposed/24 hours; and W (days/days) = the number of days of exposure/7 days. The NOAEC[ADJ] = $2 \text{ mg/m}^3 \times 6\text{h}/24\text{h} \times 5\text{d}/7\text{d} = 0.36 \text{ mg/m}^3$

Keskin et al. 2009). No chronic or carcinogenicity animal studies on perineal exposure of talc were located in the literature.

A single injection of talc (in saline) into the bursa around the ovaries of rats showed foreign-body granulomas with confirmation of the presence of talc (Hamilton et al. 1984). Daily perineal or intravaginal application of talc (in saline) to rats for 3 months produced evidence of foreign-body reaction and infections; in addition, an increase in the number of inflammatory cells were found in all genital tissues. While no cancer or pre-cancer effects were observed, Keskin and colleagues (2009) noted that the study duration may have been too short to note these types of effects.

Human studies

Several meta-analyses of available epidemiological data have been published; some very recently (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2018). These studies have consistently reported a positive association with ovarian cancer and perineal talc exposure. Taher and colleagues (2018) identified 27 studies (24 case-control and 3 cohort) for a meta-analysis; ever versus never perineal use of talc and the risk of ovarian cancer resulted in a statistically significant pooled odds ratio (OR) of 1.28 (see Table 6-1). Other published meta-analyses have demonstrated similar results, with ORs ranging from 1.22 to 1.35 (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018).

Table 6-1. Available human epidemiological studies investigating the association of perineal use of talc and ovarian cancer (Taher et al. 2018, in preparation)

Study type	Total sample size (no. of cases)	Study conclusion	OR [95% CI]	Reference
Case-control	686 (235)	Possible association in subgroup	Not included	Booth et al. 1989
Case-control	1014 (450)	Positive association	1.42 [1.08, 1.87]	Chang and Risch 1997
Case-control	336 (112)	Positive association in subgroup	Not included	Chen et al. 1992
Case-control	735 (313)	Positive association	1.60 [1.10, 2.33]	Cook et al. 1997
Case-control	430 (215)	Positive association	1.92 [1.27, 2.90]	Cramer et al. 1982
Case-control	4141 (2041)	Positive association	1.32 [1.15, 1.51]	Cramer et al. 2016
Case-control	3187 (1385)	Positive association	1.36 [1.14, 1.62]	Gates et al. 2008

Study type	Total sample size (no. of cases)	Study conclusion	OR [95% CI]	Reference
Case-control	305 (153)	No association	2.49 [0.94, 6.60]	Godard et al. 1998
Case-control	1684 (824)	Positive association	1.30 [1.10, 1.54]	Green et al. 1997
Case-control	274 (116)	No association	1.10 [0.70, 1.73]	Harlow and Weiss 1989
Case-control	474 (235)	Positive association in subgroup	1.50 [1.00, 2.25]	Harlow et al. 1992
Case-control	306 (135)	No association	0.70 [0.40, 1.22]	Hartge et al. 1983
Case-control	2704 (902)	Positive association	1.40 [1.16, 1.69]	Kurta et al. 2012
Case-control	225 (46)	No association	1.15 [0.41, 3.23]	Langseth and Kjaerheim 2004
Case-control	3085 (1576)	Positive association in subgroup	1.17 [1.01, 1.36]	Merritt et al. 2008
Case-control	1354 (249)	Positive association in subgroup	1.37 [1.02, 1.84]	Mills et al. 2004
Case-control	2143 (1086)	No association	1.06 [0.85, 1.32]	Moorman et al. 2009
Case-control	2134 (767)	Positive association in subgroup	1.50 [1.10, 2.05]	Ness et al. 2000
Case-control	123 (77)	Possible association	1.00 [0.20, 5.00]	Rosenblatt et al. 1992
Case-control	2125 (812)	Possible association	1.27 [0.97, 1.66]	Rosenblatt et al. 2011
Case-control	1329 (584)	Positive association	1.44 [1.11, 1.87]	Schildkraut et al. 2016
Case-control	389 (189)	No association	1.05 [0.28, 3.94]	Tzonou et al. 1993
Case-control	727 (188)	Possible association	1.45 [0.81, 2.60]	Whittemore et al. 1988
Case-control	1155 (462)	No association	1.00 [0.80, 1.25]	Wong et al. 1999
Case-control	1297 (609)	Positive association	1.53 [1.13, 2.07]	Wu et al. 2009
Case-control	4092 (1701)	Positive association in	1.46 [1.27, 1.68]	Wu et al. 2015

Study type	Total sample size (no. of cases)	Study conclusion	OR [95% CI]	Reference
		subgroup		
Cohort	108870 (797)	Possible association in subgroup	Not included	Gates et al. 2010
Cohort	78630 (307)	Possible association in subgroup	1.09 [0.86, 1.38]	Gertig et al. 2000
Cohort	41654 (154)	No association	0.73 [0.44, 1.21]	Gonzalez et al. 2016
Cohort	61285 (429)	No association	1.12 [0.92, 1.36]	Houghton et al. 2014

Abbreviation: CI, confidence interval.

Mode of action

The etiology of most ovarian tumours, in general, has not been well established. There are a number of different tumour types with characteristic histologic features, distinctive molecular signatures, and disease trajectories. Moreover, these tumours are heterogeneous, and they can arise from different tissues of the female reproductive tract, including the fallopian tube epithelium (National Academy of Sciences, Engineering, and Medicine 2016).

With respect to talc specifically, local chronic irritation leading to an inflammatory response is one possible mechanism of tumour progression that is frequently hypothesized (Muscat and Huncharek 2008; Penninkilampi and Eslick 2018; Taher et al. 2018). It is known that persistent indications of inflammation (including C-reactive protein, tumour necrosis factor, and other inflammatory markers) are detected in the blood of women prior to a diagnosis of ovarian tumours (Trabert et al. 2014). Increases in the number of inflammatory cells were found in all genital tissues of rats intravaginally exposed to talc for 3 months (Keskin et al. 2009). There is support for an association of inflammation and increased risk of ovarian cancer (National Academy of Sciences, Engineering and Medicine 2016; Rasmussen et al. 2017).

Talc particles were detected in the ovaries of rats that received intrauterine instillations of talc, and to a lesser extent in those that were dosed intravaginally with talc (Henderson et al. 1986). No translocation of talc into the ovaries was detected after single or multiple intravaginal applications of talc to rabbits (Phillips et al. 1978) or to monkeys (Wehner et al. 1986).

Talc particles were identified in 10 of 13 human ovarian tumours but were also found in 5 of 12 “normal” ovarian tissues removed from patients with breast cancer (Henderson et al. 1971). Ovaries from 24 patients undergoing incidental oophorectomy were examined; 12 women reported frequent perineal talc use, and the other 12 women were

non-users. Talc particles were detected in all 24 cases (both ever- and non-users) (Heller et al. 1996b). Wehner (2002) attributed the talc in the never users to (a) possible sample contamination, because some studies using negative controls resulted in particle counts similar to the test sample; and/or (b) possible false positives due to the use of a single radioactive tracer. To explain why talc is present in the never users, Heller and colleagues (1996b) hypothesized that talc use during diapering could contribute to the ovarian particle burden.

Translocation of other inert particles, similar in size to talc, has also been studied. A study in monkeys did not show any translocation of carbon black particles when a suspension was placed in the vaginal posterior fornix (Wehner et al. 1985). However, retrograde migration was detected when rabbits were administered a lubricant powder intravaginally (Edelstam et al. 1997). Other authors have noted similar transportation of particles to the upper genital tract (Egli and Newton 1961; De Boer 1972; Venter and Iturralde 1979). There are also some indications that particles can migrate from the vagina to the upper reproductive tract in humans (Egli and Newton 1961; Venter and Iturralde 1979; Heller et al. 1996a,b), and perineal exposure to talc has also been associated with a presence of talc in the lymph nodes and ovaries of women diagnosed with ovarian cancer (Heller et al. 1996a,b; Cramer et al. 2007).

Another possible mode of action that is hypothesized in the scientific literature is immune-mediated. It has been suggested that talc particles need not reach the ovaries but only need to reach the lower genital tract where talc could trigger changes (such as the production of heat shock proteins and/or decreased levels of antibodies) that could contribute to ovarian cancer (Cramer et al. 2005; Muscat et al. 2005). Human mucin 1 (MUC1) is expressed in high levels by ovarian cancer. Mucins are proteins involved in the formation of mucous barriers on epithelial surfaces (Gendler and Spicer 1995). Anti-MUC1 antibodies may have a protective effect; patients generate immunity against MUC1 produced by their tumours (Cramer et al. 2005). The Cramer et al. (2005) study used an enzyme-linked immunosorbent assay to measure anti-MUC1 antibody in women (controls; n = 721) to determine the factors that predict the presence of antibodies. It was found that the use of talc in the perineal area was associated with significantly decreased levels of antibodies to MUC1 (Cramer et al. 2005).

The most recent meta-analysis (Taher et al. 2018) employed the Hill criteria (Hill 1965) to assess the epidemiological evidence of a causal relationship. The Hill considerations are a set of factors (i.e., strength, consistency, specificity, temporality, biological gradient, biological plausibility, and coherence). These considerations form a framework for evaluating evidence in humans to help determine whether observed associations are causal (Hill 1965; Coglianò et al. 2004; US EPA 2005; Health Canada 2011; Fedak et al. 2015). Each factor, as reported in Taher et al. (2018), is elaborated upon below.

Strength: Of the 30 epidemiological studies examined by Taher et al. (2018), 15 case-control studies reported a positive association with statistical significance; 6 of these 15 had an OR of 1.5 or greater. Similarly, Penninkilampi and Eslick (2018) and Berge and colleagues (2018) each assessed 27 epidemiological studies and respectively

determined 14 and 13 case-control studies as reporting a positive association with statistical significance. In both cases, 5 of these studies had an OR of 1.5 or greater. Terry and colleagues (2013) only pooled 8 case-control studies; 5 of the 8 (63%) had a statistically significant positive association.

The individual cohort studies did not show a statistically significant association between perineal talc use and ovarian cancer (Berge et al 2018; Penninkilampi and Eslick 2018; Taher et al 2018). However, there was a positive association, with statistical significance, specific to invasive serous-type ovarian cancer in the cohort studies (OR = 1.25) (Penninkilampi and Eslick 2018). Given the long latency for ovarian cancer, the follow-up periods may not have been sufficient to capture all the cases for the individual cohort studies. Also, given the rarity of ovarian cancer, many of the available human studies may not be sufficiently powered to detect a low OR. Sample sizes were not large enough to detect a 20 to 30 % increase in risk; a group of over 200 000 women would need to be followed for over 10 years in order to detect a 20% (above background) increased risk with statistical significance (Narod 2016). With larger sample sizes, more individual studies may have demonstrated stronger associations.

Consistency: Several meta-analyses conducted over the past 15 years calculated similar ORs and resulted in similar conclusions; that there is a small yet consistent and statistically significant increased risk for ovarian cancer with perineal talc use (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al 2018). The epidemiological studies examined in these meta-analyses were conducted over different periods in time (across more than four decades), among different ethnicities, and spanned many geographical areas worldwide (Taher et al. 2018).

Specificity: Although there are many other risk factors for ovarian cancer (e.g., increased age, family history of cancer, obesity, nulliparity) (National Academy of Sciences, Engineering, and Medicine 2016), perineal talc exposure is specifically associated with cancer of the ovary and not other organs (Taher et al. 2018).

Temporality: In all case-control studies reporting positive outcomes, the participants recalled that exposure to talc preceded the reported outcome. However, in the cohort studies (reporting a lack of positive association), it is not known whether the follow-up period was adequate to detect a potential association between perineal talc exposure and ovarian cancer (Taher et al. 2018).

Biological gradient: There is a lack of an available exposure-effect relationship in the human epidemiological data. Many of the studies only assessed a single-dose level (ever versus never users). Furthermore, data with respect to the types of powder used by subjects or the amounts applied were not presented, and therefore a relationship between the concentration/dose of talc in the powder and the incidence of ovarian cancer could not be investigated. Taher and colleagues (2018) isolated seven studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc; however, none demonstrated both a clear dose-response

trend and statistical significance (Whittemore et al. 1988; Harlow et al. 1992; Mills et al. 2004; Wu et al. 2009; Rosenblatt et al. 2011; Cramer et al. 2016; Schildkraut et al. 2016).

Biological plausibility: Particles of talc are hypothesized to migrate into the pelvis and ovarian tissue, causing irritation and inflammation. The presence of talc in the ovaries has been documented (Heller et al. 1996b). This evidence of retrograde transport supports the biologic plausibility of the association between perineal talc application and ovarian exposure; however, the specific mechanism(s) and cascade of molecular events by which talc might cause ovarian cancer have not been identified (Taher et al. 2018).

Coherence: Multiple case-control studies reported a lower risk of ovarian cancer in women who underwent pelvic surgery or tubal ligation (which disrupts the pathway and movement of talc from the lower to the upper genital tract) and suppressed ovulation (as cited by Taher et al. 2018; Cramer et al. 1982, 2016; Whittemore et al. 1988; Rosenblatt et al. 1992; Green et al. 1997; Wong et al. 1999; Mills et al. 2004). As noted in Penninkilampi and Eslick (2018), the main reductions in cancer incidence with tubal ligation were for serous and endometrial tumour types but not for mucinous or clear-cell tumours. Thus, tubal ligation is only effective in reducing the incidence of the same tumour types noted to be associated with perineal talc use.

The most recent meta-analysis detailed above (Taher et al. 2018), and consistent with the Hill criteria, suggests a small but consistent statistically significant positive association between ovarian cancer and perineal exposure to talc. Further, available data are indicative of a causal effect. A clear point of departure could not be derived from the available literature; consequently, hazard characterization is qualitative in nature.

6.2 Exposure assessment

This exposure assessment focuses on routes of exposure where critical effects have been identified; namely, non-cancer lung effects following inhalation of insoluble respirable particles of talc, and an association with ovarian cancer following perineal exposure to talc.

6.2.1 Environmental media, food and drinking water

Talc is a naturally occurring mineral, and there are several deposits in Canada (Kogel et al. 2006). Currently, there is one operating open-pit mine and concentrator along with an operating mill (MAC 2016); however, no talc concentration data in ambient air or around open-pit talc mines and processing facilities have been reported. Although particulate matter (PM) information for inhalable and respirable particles is available in the vicinity of these facilities (NPRI 2018), these data were not used in the exposure assessment as PM released from facilities is expected to contain a mixture of substances, hence the concentration would not reflect talc exposure from this source. However, given the

limited number of industrial and commercial sites producing and processing talc in Canada, talc exposure from ambient air is not expected to be significant.

Talc is insoluble in water (Table 3-1) and is expected to settle out during water treatment; exposure to the general population from drinking water is not expected.

There is potential for oral exposure resulting from the use of talc as a food additive; however, exposure from these uses is expected to be minimal (email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 27, 2018; unreferenced). Exposure from the use of talc as a component in food packaging materials is expected to be negligible (email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 27, 2018; unreferenced). Exposure from the oral route was not quantified because no critical health effects from the oral route of exposure have been identified. The JECFA has assigned an ADI of “not specified” for talc on the basis of low toxicity, and talc is “generally recognized as safe” as a food additive in the United States (JECFA 2006; U.S. FDA 2015).

6.2.2 Products available to consumers

Talc is present in approximately 8500 self-care products in Canada, including approximately 200 non-prescription drug products, approximately 2000 natural health products, and approximately 6500 cosmetic products. In addition, there are approximately 1300 prescription drugs containing talc. There is potential for oral exposure resulting from the use of self-care products and non-OTC drugs (including prescription, controlled substances, and ethical drugs) as a medicinal and non-medicinal ingredient containing talc. However, exposure from the oral route was not quantified as no critical health effects from the oral route of exposure have been identified.

There is the potential for dermal contact with talc from the use of self-care products. Systemic exposure resulting from dermal contact with talc is expected to be negligible as it is not expected that talc will be absorbed on the basis of its physical-chemical characteristics as an insoluble solid particle. In addition, a dermal health effect endpoint has not been identified for talc.

Notifications submitted under the *Cosmetic Regulations* to Health Canada for talc, the LNHPD (modified 2018), the Drug Product Database (DPD), voluntary information submitted to Environment and Climate Change Canada and Health Canada (ECCC, HC 2017), publicly available databases and websites (e.g., Household Products Database 1993-; CPCat 2014; CPID 2017), and material safety and technical datasheets were used to identify products where there is: (a) the potential for inhalation of insoluble respirable talc, and (b) the potential exposure to the perineal region. These products and associated exposures are presented below.

No inhalation or perineal exposures were identified with respect to the major commercial or industrial uses of talc in paper, plastics, ceramics, and putties.

Inhalation exposure

For inhalation exposure, potential exposures were focused on products that were formulated as loose powders and were available to consumers, which included approximately 400 self-care products (primarily cosmetics). Products formulated as pressed powders, which comprise the majority of cosmetics containing talc (approximately 4000 products) were not identified as a potential source of exposure of concern because the formation of a “dust cloud” available for inhalation is not expected during the use of these products. Available information of interest were self-care products marketed as cosmetics, NHPs, or non-prescription drugs that are intended for application to the body, face, feet, buttocks (babies), and hair (e.g., dry hair shampoo). Concentrations of talc range from less than 10 to 100 % in these types of products.

In order to determine if talc loose-powder self-care products contain respirable particles, Health Canada measured the particle size distribution of three products (one baby powder and two adult body powder products) containing high concentrations of talc (>90%) available in Canada (Rasmussen 2017). Using an Aerodynamic Particle Sizer, the particle size distribution for the three products ranged from < 0.5 µm to 8 µm, with median particle sizes ranging from 1.7 to 2 µm. Thus, all of the particles were within the inhalable range (< 10 µm), and the median particle size was within the respirable range (< 4 µm). Number concentrations measured using a scanning mobility particle sizer indicated that the proportion of nano-sized particles (<100 nm) was small (< 10 %) to negligible, depending on the product.

Several studies were conducted by the cosmetic industry in the 1970s to provide data required to assess the safety of talc powder products and generate air concentrations (Aylott et al. 1979; Russell et al. 1979). These studies demonstrated that during the use of face, baby, and adult powders, there are quantifiable concentrations of respirable talc particles available for inhalation exposure. In 1978, Aylott and colleagues determined mean respirable air concentrations of 0.48 to 1.9 mg/m³ of talc (< 7 µm) over 5 minutes for loose face powder, adult dusting powder, baby dusting powder, and micronized adult dusting powder. That same year, concentrations of talc (< 10 µm) of 0.19 mg/m³ and 2.03 mg/m³, respectively, were determined near the infant breathing zone during a simulation of routine application of talcum powder during diapering, and in the breathing zone of adults during the application of talcum powder to their body (Russell et al. 1979). In both of these studies, the highest air concentrations were associated with the adult application of talcum powder to their bodies over infant diapering and application of loose facial powder. There are uncertainties with the calculated talc concentrations determined from these studies due to limitations in the collection and analysis of talc concentrations on the basis of the use of older equipment, older sampling methods, and older talc products.

In 2017, a study assessing the health risk from the use of cosmetic talc from historical products was published (Anderson et al. 2017). This study included examining historical talc products from the 1960s and 1970s to characterize airborne respirable dust concentrations during the use of these products. To quantify respirable talc concentrations in the breathing zone, Anderson and colleagues (2017) designed a study where 5 volunteers were asked to apply historical talc products as they typically would in a bathroom setting. Cyclone air sampling devices were attached to the breathing zone of each volunteer. Each exposure simulation consisted of 8 application events, at six-minute intervals, for a total sampling duration of 48 minutes. This study design ensured that the sample mass on the sampling filter was large enough for quantification and accuracy, but it was not expected that during the typical use of a talc body powder that individuals apply talc every six minutes over a 48-minute window. Average talc concentrations over the 48-minute exposure simulation were calculated using the total measured mass (from 8 applications over 48 minutes) and the air volume over the entire 48-minute sampling period. Respirable talc concentrations ranged from 0.26 to 5.03 mg/m³, and the average was 1.46 mg/m³. The average air concentration by subject ranged from 0.44 to 3.28 mg/m³. Respirable talc concentrations were more variable between subjects than within subjects, suggesting that individual behaviour has a strong influence in airborne concentrations.

In 2018, Health Canada conducted a small study in order to measure the air concentrations of particles in the breathing zone of adult volunteer subjects while they were applying talc-containing self-care products (Rasmussen 2018). Continuous, direct-reading, personal breathing-zone monitors (positioned beside the nose) measured average particulate matter of aerodynamic diameter of 4 µm or less (PM₄) concentrations of 0.48 ± 0.18 mg/m³ and 1.80 ± 0.82 mg/m³ for volunteers applying body powder and loose face powder, respectively. Subjects repeated the application in triplicate. These average concentrations fall within the range of concentrations measured by Anderson and colleagues (2017). In this study, the application of loose face powder resulted in the highest average air concentration in the immediate vicinity of the nose.

Several exposure scenarios were derived to characterize inhalation exposure to talc particles from the use of self-care products; namely, the use of baby, body, face, and foot powders (loose formulations), and dry hair shampoo. Average air concentrations by subject from Anderson et al. 2017 were combined with the body and face replicates from Rasmussen 2018 to obtain an overall average air concentration of 1.36 ± 0.97 mg/m³. This value was used to estimate adjusted air concentrations for self-care products based on the highest concentration of talc present in these products. The results are summarized in Table 6-2. The inputs for each of these scenarios are outlined in Appendix A.

Table 6-2. Inhalation exposure estimates to talc from self-care products available to consumers

Product type	Age group	Concentration in air per event (mg/m³)^a	Adjusted exposure concentration (mg/m³)^b
Baby powder 100% talc	Infant and Adult	1.36	0.0071
Body powder 100% talc	Adult	1.36	0.0047
Face powder 100% talc	Adult	1.36	0.0047
Foot powder 97% talc	Adult	1.32	0.0034
Dry hair shampoo 100% talc	Adult	1.36	0.0011

^a Average measured air concentrations (Anderson et al. 2017, Rasmussen 2018) × the highest concentration of talc in product type.

^b Refer to Appendix A for details.

Perineal exposure

Several types of self-care products have the potential to result in exposure to the perineal region. There are several baby and body powders (approximately 50 products) with concentrations of talc that range from 0.3 to 100 %. There has been a decline in popularity of the use of talc for feminine hygiene practices over time; of 6000 North American women, 19 % of women born between 1920 and 1940 reported applying talc directly to the perineal region, but only 3% of women born after 1975 reported the same (Narod 2016). Houghton and colleagues (2014) reported that in 2001, the proportion of U.S. women who were users of perineal talc was estimated at 40 %, down from 52 % during 1993 to 1998.

There is a small number of diaper or rash cream self-care products (less than 10) which contains low concentrations of talc as a non-medicinal ingredient (up to 0.5 %). Talc is permitted as a medicinal ingredient in diaper rash products at concentrations from 45 to 100 % (Health Canada 2007); however, there are no diaper rash products listed in the LNHPD containing talc as a medicinal ingredient (LNHPD [modified 2018]).

Additional self-care products that have the potential for perineal exposure (approximately 100 products) include antiperspirants and deodorants (e.g., genital antiperspirants), body wipes, bath bombs, and to a lesser extent (due to wash off or removal) other bath products (i.e., soap, shower gel) and products associated with hair removal (e.g., epilatory products). These products are formulated as gels, sprays, loose powders, and solid cakes, and range in concentration from less than 1% to 100% talc.

As indicated in Section 4, there is no evidence to suggest that talc is currently being used as a dry lubricant on condoms or medical examination gloves in Canada. At present, these are not considered to be sources of perineal exposure.

As a quantitative point of departure could not be derived from the available literature, perineal exposure from the use of self-care products was not quantified.

6.3 Characterization of risk to human health

Consistent with other international regulatory and advisory bodies (Danish EPA, U.S. EPA, MAK-Commission, U.S. FDA, and JECFA), no critical health effects were identified via the oral or dermal routes of exposure. As such, oral exposure to talc resulting from food intake and use of self-care products are not of concern.

Critical health effects have been identified following inhalation exposure to respirable talc particles. From the available toxicological studies, a NOAEC of 2 mg/m³ from the NTP inhalation studies in mice and rats was identified in which non-cancer lung effects, with lung overload, were noted at the next highest concentration of 6 mg/m³.

The average air concentration of talc following the use of a loose-powder self-care product (1.36 mg/m³) provides a small margin of exposure (i.e., 1.5) to the NOAEC of 2 mg/m³. However, the NOAEC is derived from a study with an exposure profile of 6 hours per day, 5 days per week, over 4 weeks, while the actual exposure scenarios from the use of self-care products are intermittent, occurring in minutes per day, daily, or weekly over many years. To address the differences in exposure between the NTP study and the actual use pattern, both the NOAEC and the talc air concentrations were adjusted to a continuous exposure scenario according to U.S. EPA guidance on inhalation risk assessment to more accurately characterize potential risk (U.S. EPA 1994, 2009). The NOAEC of 2 mg/m³ is equivalent to an adjusted concentration of 0.36 mg/m³, as noted in the Health Effects section. The NOAEC of 2 mg/m³ was extracted from a 4-week inhalation study as a NOAEC for chronic exposure was not available. Episodic exposures from product use are expected to increase lung load due to the long alveolar clearance of talc. The adjusted air concentrations from the use of self-care products are presented in Table 6-3.

Table 6-3. Relevant exposure and hazard values for talc, and margins of exposure, for determination of risk

Exposure scenario	Adjusted air concentration, CA (mg/m ³) ^a	Adjusted critical-effect level (mg/m ³)	Critical health effect endpoint	MOE
Baby powder 100% talc	0.0071	NOAEC[adj]: 0.36	non-cancer lung effects	50

Body powder 100% talc	0.0047	NOAEC[adj]: 0.36	non-cancer lung effects	76
Face powder 100% talc	0.0047	NOAEC[adj]: 0.36	non-cancer lung effects	76
Foot powder 97% talc	0.0034	NOAEC[adj]: 0.36	non-cancer lung effects	106
Dry hair shampoo 100% talc	0.0011	NOAEC[adj]: 0.36	non-cancer lung effects	327

Abbreviations: adj, adjusted; CA, concentration in air per event; MOE, margin of exposure.

^a From Anderson et al. (2017) and Rasmussen (2018), respectively, based on the highest concentration in products. For most of these product types, there is a wide range of talc concentrations (< 10 to 100 %).

The margins of exposure (MOEs) between the adjusted critical-effect level and the adjusted air concentrations range from 50 to 327 for self-care products. The MOEs for baby powder, body powder, face powder, and foot powder are considered potentially inadequate to account for uncertainties in the health effects (including a lack of a NOAEC from chronic studies) and exposure databases. The MOE for dry hair shampoo is considered adequate to address uncertainties in the health effects and exposure databases.

Based on available human data, ovarian cancer was also identified as a critical health effect for the perineal route of exposure to talc. There is the potential for perineal exposure to talc from the use of various self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs). As noted in the Health Effects section, a point of departure cannot be derived for this health effect. Data from published meta-analyses of epidemiological studies indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2018). As noted by Narod (2016), "It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer it is likely to be causal." Similarly, Penninkilampi and Eslick (2018) noted that "the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association." Taher and colleagues (2018) noted that "consistent with previous evaluations by the International Agency for Research on Cancer (2010), and more recent and subsequent evaluations by individual investigators (Penninkilampi and Eslick 2018; Berge et al. 2018; Terry et al. 2013), the present comprehensive evaluation of all currently available relevant data indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans."

The meta-analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. Further, available data are indicative of a causal effect. Given that there is the potential for perineal exposure to talc from the use of various self-care products, a potential concern for human health has been identified.

6.4 Uncertainties in evaluation of risk to human health

The inhalation of talc has been associated with a variety of non-cancerous lung effects, commonly termed talcosis. Dose-response data for lung effects in humans is, for the most part, lacking, and the use of animal data to quantify risk due to talc inhalation is considered appropriate. Despite the lack of exposure quantification, there are numerous case reports, as well as worker studies, that have identified non-cancer health effects from inhalation of talc powders. There is some uncertainty regarding the extrapolation of the NOAEC identified in animal models exposed for 6 hours per day for a short duration (4 weeks) to long-term episodic human exposures. The true NOAEC for chronic exposure is likely substantially lower than 2 mg/m³.

Some self-care products, in particular, some face powders, may contain a cover or another mechanism that would reduce the potential for the generation of a particle or dust cloud, or that would reduce the concentration of the dust cloud during use of the product. There is uncertainty as to which products, and the proportion of products on the market, that incorporate these exposure-mitigation measures.

There are limitations with the human epidemiological data. Potential sources of bias include selection bias due to low response rates or from limiting subjects, and exposure misclassification due to recall bias (Taher et al. 2018). Muscat and Huncharek (2008) also proposed that symptoms of ovarian cancer prior to diagnosis may increase the perineal use of talc and bias the results. However, Narod (2016) and Berge and colleagues (2018) put less emphasis on recall bias. In studies where the exposure is simple (e.g., never versus ever use), recall bias is unlikely to be an important source of bias (Narod 2016). The positive association is strongest for the serous histologic type (Berge et al. 2018; Taher et al. 2018); findings that the association may vary by histologic type detracts from the hypothesis of report bias, as this type of bias would likely operate for all histologic types (Berge et al. 2018).

Ovarian cancer, in general, is not well understood (National Academy of Sciences, Engineering, and Medicine 2016), and a comparable animal model is not available. Health Canada has identified self-care products with the potential for perineal exposure (e.g., baby powder, body powders, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs); however, there is no indication exactly how the products are being used, the extent to which they would contribute to perineal exposure, and with what frequency and amount.

Talc use during diapering is a confounder that was not adequately accounted for in the epidemiological studies. It has not been determined whether the internal female genital

tract is exposed to talc dusts during infancy (Muscat and Huncharek 2008). As well, not all the available human studies are clear as to the formulations used for perineal applications. It is possible that the identified cancer incidences are specific to loose-powder formulations; however, there is inadequate information to attribute the cancer incidences to other formulation types (e.g., creams).

7. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from talc. It is proposed to conclude that talc does not meet the criteria under paragraphs 64(a) or (b) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that talc meets the criteria under paragraph 64(c) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that talc meets one of the criteria set out in section 64 of CEPA.

Talc is proposed to meet the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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Appendix A. Inhalation exposure estimates

Table A-1. Estimated inhalation exposure concentrations from self-care products containing loose powder talc available to consumers

Scenario	Talc product conc. ^a	Study ^b conc. (mg/m ³)	CA ^b (mg/m ³)	ET ^c (hr/d)	EF ^d (d/yr)	ED ^e (yr)	EC adjusted (mg/m ³) ^b
Baby powder, infants	100 %	1.36	1.36	0.125	365	4	0.0071
Baby powder, adults	100 %	1.36	1.36	0.125	365	8	0.0071
Body powder, adults	100 %	1.36	1.36	0.083	365	58	0.0047
Face powder, adults	100 %	1.36	1.36	0.083	365	58	0.0047
Foot powder, adults	97 %	1.36	1.32	0.083	274	58	0.0034
Dry hair shampoo, adults	100 %	1.36	1.36	0.083	84	58	0.0011

Abbreviations: Conc., concentration; CA, concentration in air per event; ET, exposure time; EF, exposure frequency; ED, exposure duration; EC, adjusted exposure concentration.

^a Highest concentration of talc found per product type from notifications submitted under the *Cosmetic Regulations* to Health Canada for talc, DPD [modified 2018], email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017, unreferenceed; LNHPD [modified 2018], email from the Non-prescription and Natural Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017, unreferenceed; Fiume et al. 2015; Household Product Database 1993-; CPCat 2014; CPID 2017; SDS Search Tool 2016.

^b Average by subject from Anderson et al. 2107 and Rasmussen 2018 (unpublished). CA = average study concentration × maximum talc concentration in product.

^c ET is 5 minutes/application based on median time spent in the bathroom following a shower or bath (U.S. EPA 2011) × number of applications/day, whereby baby powder assumes 1.5 applications/day (CTFA 1983); the rest assume 1 application/day.

^d EF is assumed to be daily for baby, body (U.S. EPA 2011) and face powder (Ficheux et al. 2015); foot powder 0.75 times/day or 274 times/year (Ficheux et al. 2015); dry hair shampoo 0.23 times/day or 84 times/year (Ficheux et al. 2015).

^e Assumed infant wears diapers up to 4 years, adult exposure to baby powder from diapering children, 4 years per child and assume 2 children per family (Statistics Canada 2016), adult exposure for body powder, and foot powder (80 years lifetime, 12 years child).

^f Adjusted exposure concentration is calculated as per Equation 8 in the U.S. EPA 2009 guidance document "Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual," where $EC = (CA \times ET \times EF \times ED)/AT$, and AT = averaging time, which is on the basis of $ED \times 365$ days/year × 24 hours/day.